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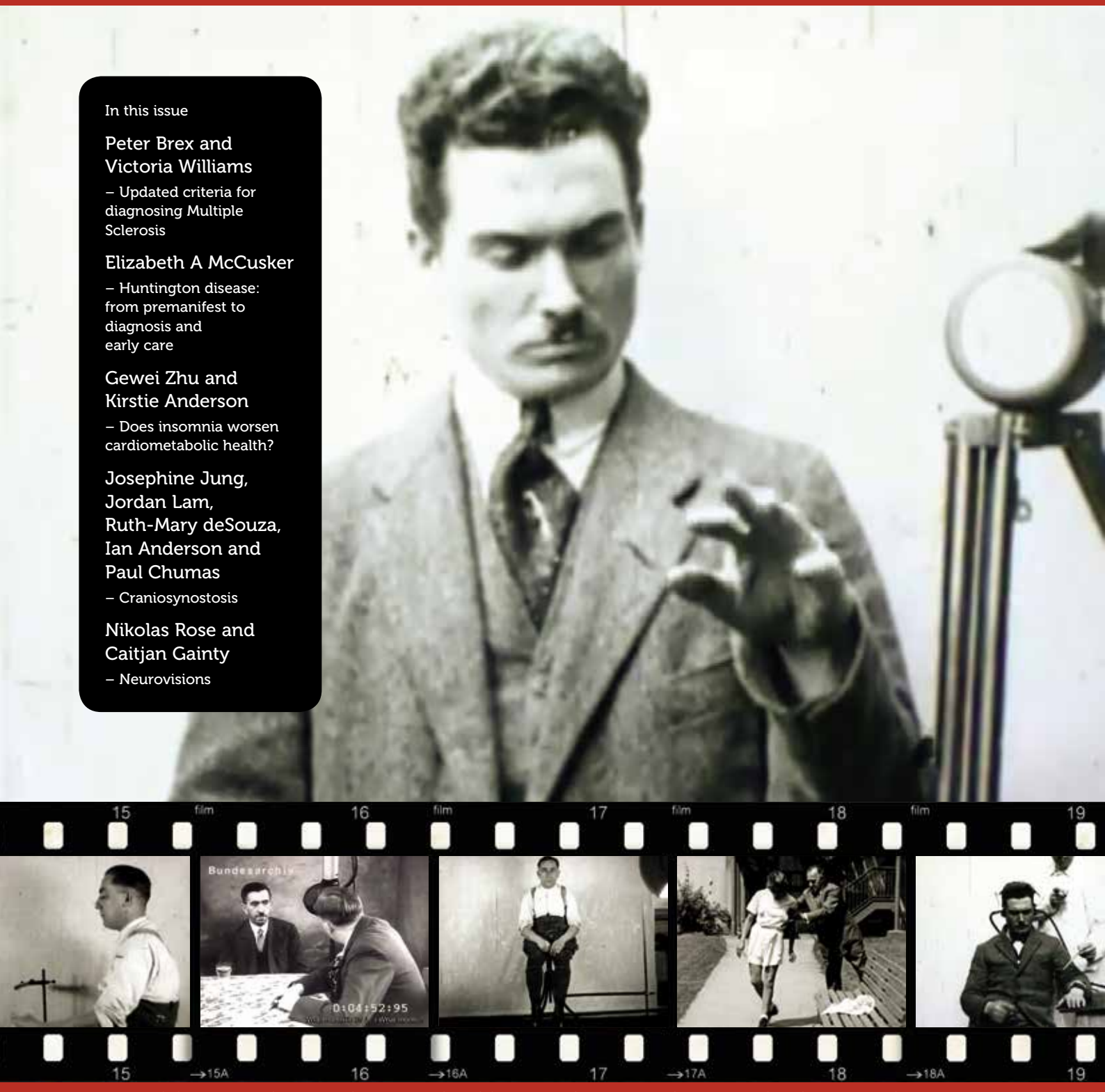
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

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Welcome to MAVENCLAD®

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REFERENCES: 1. MAVENCLAD® Summary of Product Characteristics. Merck; **2.** Giovannoni G, *et al. N Engl J Med* 2010;362:416–426; **3.** Giovannoni G, *et al. N Engl J Med* 2010;362:416–426 (supplementary information); **4.** Giovannoni G, *et al. Mult Scler.* 2017;doi:10.1177/1352458517727603.

PRESCRIBING INFORMATION – UK AND IRELAND
MAVENCLAD® cladribine (Please refer to the full Summary of Product Characteristics before prescribing)
PRESENTATION: Cartons of 1, 4 or 6 tablets. Each tablet contains 10 mg of cladribine. **INDICATIONS:** Treatment of adults with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. **DOSAGE AND ADMINISTRATION:** Must be initiated and supervised by a physician experienced in MS treatment. Recommended cumulative dose: 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year. Each course comprises 2 treatment weeks, one at the start of the first month and one at the start of the second month of each year. Each treatment week comprises 4 or 5 days on which the patient receives 10 mg or 20 mg as a single daily dose, depending on body weight. For details, see dosage tables in the SPC. 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Screen for latent infections prior to initiation in years 1 and 2. Delay initiation in latent or acute infection until treated. Varicella zoster vaccination is recommended in antibody-negative patients prior to treatment initiation. Delay initiation for 4-6 weeks following vaccination. Consider anti-herpes prophylaxis during grade 4 lymphopenia. If lymphocyte count falls below 500 cells/mm^3, actively monitor for symptoms suggestive of infection and initiate anti-infective treatment accordingly. Interrupt or delay MAVENCLAD until infection has resolved. Perform baseline MRI before initiating MAVENCLAD (usually within 3 months). Evaluate benefit-risk prior to initiation in patients with previous malignancy. Advise patients to follow standard cancer screening guidelines. Exclude pregnancy before initiation in years 1 and 2. Before initiation in year 1 and 2, counsel male and female patients on potential for risk to the foetus and need for effective contraception. Contraception should be used by both male and female patients during treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraception should add barrier method during treatment and for at least 4 weeks after last dose in each treatment year. In patients previously treated with immunomodulatory or immunosuppressive products, consider their mode of action and duration of effect before initiation of MAVENCLAD. Consider an additive effect on the immune system when such products are used after treatment with MAVENCLAD. When switching from another MS agent, perform a baseline MRI. In patients requiring blood transfusion, irradiation of cellular blood components is recommended prior to administration. Not to be taken by patients with hereditary fructose intolerance. Separate administration of any other oral medicinal product by at least three hours from MAVENCLAD administration. Concomitant treatment with other disease-modifying treatments for MS not recommended. Monitor haematological parameters when taken with other substances that affect the haematological profile. Do not initiate treatment within 4-6 weeks of live or attenuated live vaccines. Avoid vaccines during and after treatment while white blood cells not within normal limits. Avoid co-administration of ENT1, CNT3 or BCRP inhibitors during the 4-5 day treatment period. Consider possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered. **SIDE EFFECTS: Very common**: Lymphopenia **Common**: Oral herpes, dermatomal herpes zoster, decreased neutrophils, rash, alopecia **Other side effects**: Tuberculosis. In clinical studies and long-term follow-up, malignancies were observed more frequently in cladribine-treated patients compared to placebo. Prescribers should consult the Summary of Product Characteristics in relation to other side effects. **LEGAL CATEGORY:** POM. **PRICE:** Pack of 1 tablet: £2,047.24 Pack of 4 tablets: £8,188.97 Pack of 6 tablets: £12,283.46 For prices in Ireland, consult distributor Allphar Services Ltd. **Marketing Authorisation Holder and Numbers:** Merck Europe B.V., Gustav Mahlerplein 102,1082 MA Amsterdam, The Netherlands; EU/1/17/1212/001, 002 & 004 **For further information contact: UK:** Merck Serono Ltd, Bedfont Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono (Ireland) Limited, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590. **Date of Preparation:** August 2018 **Job No**: UK&IE/CLA/0818/0089

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Job No: UK&IE/CLA/0817/0072k(1) Date of preparation: October 2018

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

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Biogen

Biogen wins sixth Prix Galien award

Biogen has won the Orphan Product Award at UK Prix Galien 2018, for Spinraza®, which in 2017 became the first and only approved treatment for 5q spinal muscular atrophy (SMA). This is further recognition of the innovative science behind the development of nusinersen, which has already won five Prix Galien awards in the U.S, Italy, the Netherlands, Belgium-Luxembourg and Germany. In addition, the scientists behind nusinersen won the Breakthrough Prize, which honours transformative advances toward understanding living systems and extending human life, earlier this month.

To learn more, see www.biogen.uk.com

UK PARKINSON'S Excellence Network

Nominations for the Parkinson's Excellence Awards now open

The 2019 Awards ceremony will form part of the first UK Parkinson's Excellence Network conference on 16th May 2019. If you work directly with people with Parkinson's, you can enter your service for an Excellence Network Award. If you know of a great service, you can also nominate them.

Deadlines: nominations – Thursday 31 January 2019 (midnight); Entries – Thursday 28 February, 2019.

www.parkinsons.org.uk/professionals/excellence-network-awards

The Children's Trust Wins Award at BMA Patient Information Awards

The Children's Trust was honoured with a top award at the BMA Patient Information Awards on the 25th of September. The charity, which supports children with brain injury across the UK, had two of its resources, a short film and a handbook, recognised as exceptional and powerful information sources at the ceremony which took place at BMA House, London.
The charity's short film 'From Me to You' won the User Engagement Award, with judges noting it as 'powerful' and 'heart-warming'. The film was created with three families telling their experiences honestly and openly to help future children and families going to the centre for neurorehabilitation with what they can expect while they are there.

Also recognised at the awards was The Children's Trust book 'Me and My Brain'. This book, which gives advice and guidance to teenagers affected by brain injury, was awarded Runner Up in the Information for Young Adults Award, and shortlisted for the User Engagement Award.

For more information contact:
www.thechildrenstrust.org.uk

Todd Hardy Co-Editor.

Welcome to the latest issue of ACNR. In this issue, Peter Brex and Victoria Williams from London summarise the history of MS diagnostic criteria and provide an update on the key features of the 2017 Revisions of the McDonald Criteria, including the resurgence of a role for CSF examination for oligoclonal bands to facilitate earlier diagnosis in a subset of patients who would formerly have been labelled as having a clinically isolated syndrome of demyelination.

Elizabeth McCusker from Sydney discusses important early findings in patients with pre-manifest Huntington's disease (HD), and contemplates why it may be worth making an earlier diagnosis of HD.

Gewei Zhou and Kirstie Anderson from Newcastle, UK review and explore the association between sleep disorders and cardiovascular health.

Our neurosurgical article is from Josephine Jung, Jordan Lam, Ruth-Mary deSouza, Ian Anderson and Paul Chumas, who comprehensively summarise the clinical diversity, aetiology, diagnosis and treatment of the craniosynostoses.

Our ABNT article from Helen Grote from London details how she is acquiring important extracurricular skills as part of her neurology training, discussing her role in the Medical Practitioners Tribunal Service, and informing other trainees of how to gain experience sitting on committees that shape our profession.

Sociologist, Nikolas Rose, and historian, Caitjan Gainty from London write an interesting piece contemplating how neurologists "see" their patients and how this might evolve over time, using the films of mid-20th century Psychiatrist and Neurologist, Kurt Goldstein as a starting point.

Also in this issue, JMS Pearce from Hull reminds us of Sigmund Freud's origins as a neurologist and draws attention to some of his more significant, but neglected contributions to neurology. AJ Larner from Liverpool engagingly and critically appraises the updated NICE dementia guidelines.

Multiple sclerosis presenting as a homonymous hemianopia is the subject of our case report from Nada El Youssef, Mounir Khoury, Joseph Saade, Aline Mourad and Nancy Maalouf from Lebanon.

Finally, we have the latest conference reports and book reviews. We hope you enjoy this edition of ACNR.

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Todd Hardy, Co-Editor
Email. Rachael@acnr.co.uk

Editorial board and contributors

Dr Michael Zandi PhD FRCP is an Honorary Consultant Neurologist and Honorary Senior Lecturer at the University College London, Queen Square Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG and supported by the UCLH NIHR Biomedical Research Centre.

Todd Hardy Dr Todd Hardy BSc (Hons 1), PhD, MBBS, FRACP, is Co-Editor of ACNR and is a Staff Specialist Neurologist at Concord Repatriation General Hospital, Clinical Senior Lecturer in Neurology at the University of Sydney, and Co-Director of the MS Clinic at the Brain and Mind Centre. His main interests are multiple sclerosis and other immune-mediated central nervous system disorders.

Ann Donnelly MB ChB BSc (Clin Neurosci) MRCP is Co-Editor of ACNR and a Neurology Registrar at the National Hospital for Neurology and Neurosurgery. She completed undergraduate training at University of Glasgow Medical School, with Neurology postgraduate training at Kings College Hospital, National Hospital for Neurology and Neurosurgery, and Guys and St Thomas'. She is interested in NeuroRehabilitation with a focus on patients with multiple sclerosis.

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

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

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

Rhys Davies MA, BMBCh, PhD, MRCP, is Editor of our Book Review Section. He was accredited as a Consultant Neurologist on the specialist register in 2009 and is currently a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Ysbyty Gwynedd in Bangor, North Wales. He has a clinical and research interest in cognitive neurology.

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

David Werring FRCP, PhD, FESO, is ACNR's Stroke Editor. He is Professor of Clinical Neurology at UCL Institute of Neurology, Queen Square, and Honorary Consultant Neurologist at University College Hospital and The National Hospital, Queen Square.

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

Alastair Wilkins PhD, is our Case Report Co-ordinator and is Reader in Neurology, University of Bristol and Consultant Neurologist at Frenchay Hospital, Bristol. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

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

Angelika Zarkali MBBS (Hons), MRCP, is the Editor of our Conference News section. She is a Specialist Registrar in Neurology in Kent Surrey and Sussex Deanery and has an interest in neurodegeneration and cognitive disorders.

Craniosynostosis

Josephine Jung
graduated from Medical School in Berlin in 2014. After completing her M.D. Thesis in Berlin she moved to London and is working as a Clinical Research Fellow in Neurosurgery at King's College Hospital London.

Jordan Lam
is an Academic Foundation Trainee in the East Midlands. He is pursuing a career in neurosurgery.

Ruth-Mary deSouza
obtained her medical degree in 2008 from King's College London and her MRCS in 2010.

Ian Anderson
is a Consultant Neurosurgeon at Leeds General Infirmary. Having trained in Leeds, he has previously undertaken a Neurovascular Fellowship at King's College Hospital.

Paul Chumas
is a Consultant Paediatric Neurosurgeon in Leeds General Infirmary.

Correspondence to:
Josephine Jung,
Department of Neurosurgery,
King's College Hospital, London, UK.

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Abstract
Craniosynostosis is a group of conditions characterised by the premature fusion of one or more cranial vault sutures. This may lead to abnormal cranial development with severe skull and craniofacial deformities and if the condition is left untreated, other complications such as raised intracranial pressure and cranial growth restriction may be implicated.

Craniosynostosis can arise as part of a genetic syndrome, or nonsyndromically where the pathophysiology remains less clear. Occurring in 1 in 2,000 to 2,500 live births, diagnosis is carried out shortly after birth and treatment of craniosynostosis mostly involves surgery varying from less invasive procedures in those patients diagnosed early to single or repeated open calvarial reconstruction in the more complex cases.

This article reviews the different types of craniosynostosis with their variable presentations, underlying genetic mutations, associated complications and neuro-psychological outcomes before discussing its management with distinct emphasis on surgical treatment options within a multidisciplinary team.

Introduction
Craniosynostosis is a group of conditions characterised by premature fusion of one or more of the cranial vault sutures. This can lead to abnormal cranial development and give rise to severe skull and craniofacial deformities. Craniosynostosis can arise as part of syndromes, with specific gene mutations resulting in other non-cranial manifestations in addition to synostosis, or nonsyndromically where the pathophysiology remains less clear. Both types of craniosynostosis can be familial or sporadic. Occurring in 1 in 2,000 to 2,500 live births,[1-3] infants are diagnosed at birth or within a few months thereafter[4] and should preferably have treatment within their first year of life.[5] If the condition is left untreated, craniosynostosis can lead to further deformity and other complications such as raised intracranial pressure[6-7] and cranial growth restriction. The treatment mostly involves surgery varying from less invasive procedures in those patients diagnosed early[8-10] to single or repeated open calvarial reconstruction in the more complex cases.[11,12] There are a number of clinicians involved in the care of children with this condition, highlighting the importance of a multidisciplinary team. This article will review the different types of craniosynostoses with their variable presentations, the underlying genetic mutations, complications and neuro-psychological outcomes before discussing its management with distinct emphasis on surgical treatment options within a multidisciplinary team.

Embryology
The human cranium is divided into the neurocranium housing the brain, and the viscerocranium, comprising the face. The neurocranium forms from embryonic mesenchyme of neural crest (frontal bone) and paraxial mesoderm (parietal bone) origin,[13] which surrounds the brain and forms primary ossification centres termed bone spicules. Each island of mineralised tissue migrates and undergoes intramembranous ossification to form the plates of the neurocranium. These plates remain separated in early infanthood, allowing for passage during labour and continued growth of the brain after birth. The metopic suture fuses between 3 to 9 months whilst the sagittal, coronal and lambdoid sutures do not stop growing until the second decade and eventually fuse within the third decade.[14-16] Each plate approaches one another but remains separated by the formation of a suture: the two halves of the frontal bone by the metopic suture; the frontal and parietal bones by the sagittal suture; the two halves of the parietal bone by the coronal suture; and the parietal and occipital bones by the lambdoid suture. Fontanelles, namely membrane-covered "soft spots", are located at the intersection of sutures: the larger anterior fontanelle at the intersection of the metopic, coronal and sagittal sutures and the smaller posterior fontanelle at the intersection of the sagittal and the lambdoid sutures. These fontanelles usually fuse by the age of 18 months and 3 to 6 months respectively.[14]

Types
Premature fusion of the sutures implicates that the normal growth of the neurocranium is arrested at one or more sites. In order to accommodate the growing brain, compensatory growth occurs at other sites leading to abnormal cranial development and deformity. This was described in 1851 through Virchow's law that states that if a suture prematurely fuses, growth is arrested perpendicular to the suture and is increased parallel to it.[17,18] Thus, it explains the characteristic and predictable patterns of cranial growth that occur as a result of the premature fusion of distinctive sutures (see Figure 1, adapted from Senarath-Yapa et al., 2012[19]).

Sagittal synostosis is the most common type, accounting for 40-55% of nonsyndromic craniosynostosis.[17,20] Caused by premature fusion of the sagittal suture, growth is arrested in the transverse direction and increased in the anteroposterior direction, resulting in an anteroposterior elongation with frontal bossing and occipital prominence. This characteristic "long boat" shape skull is termed scaphocephaly (derived from *skaphos*: Greek term for skiff).

Coronal synostosis has been superseded

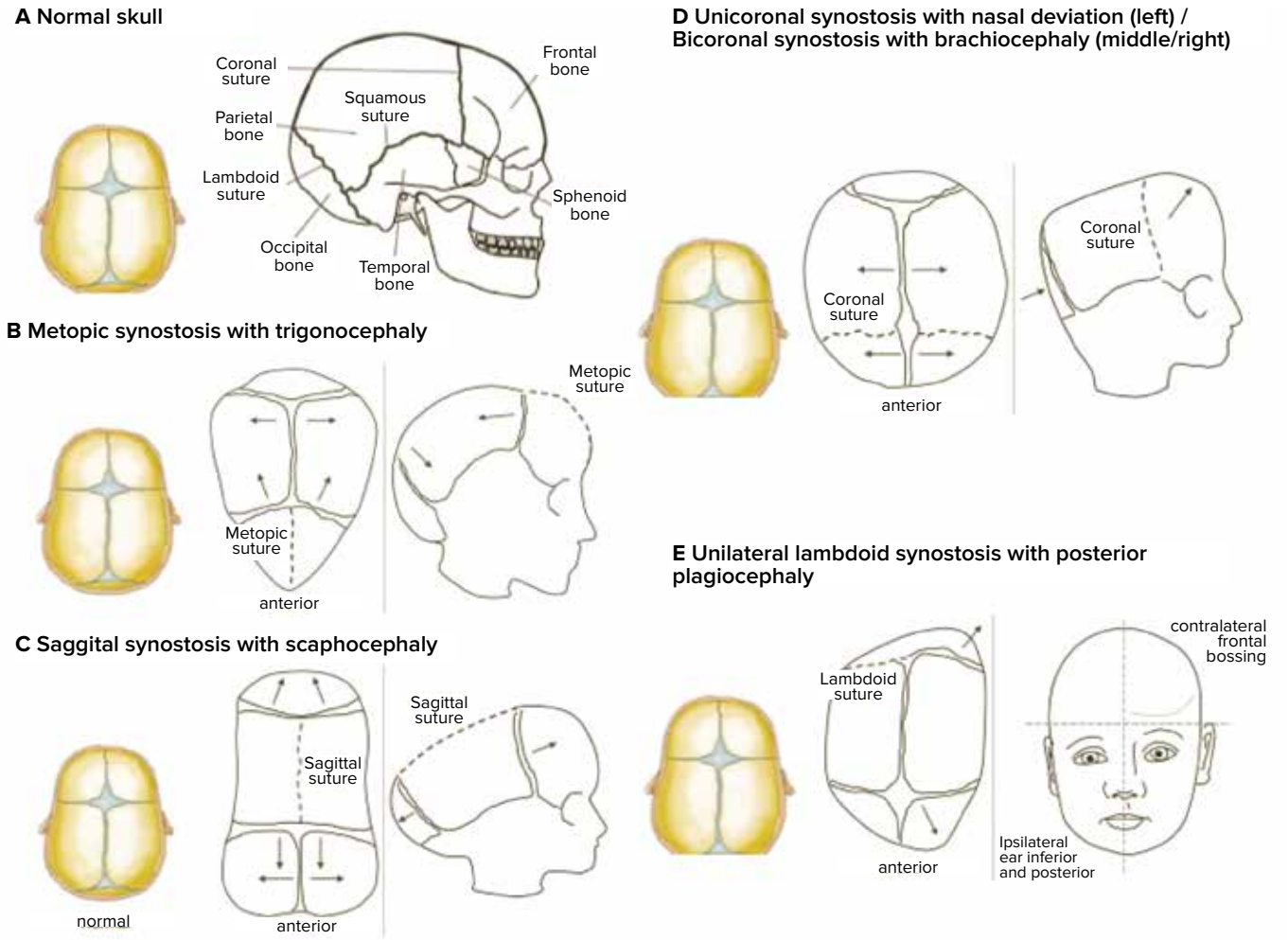

Figure 1. Cranial sutures and deformity of single suture craniosynostosis. With permission from Senarath-Yapa.

by metopic as the second most common nonsyndromic synostosis as several studies have shown over the past decade.[3,21,22] It occurs in 20-24% of nonsyndromic cases[23,24] and can be either unilateral or bilateral.

Premature fusion of the coronal suture bilaterally produces the opposite pattern of abnormal growth to sagittal synostosis, arresting growth in the anteroposterior direction and increased growth in the transverse direction, producing a short wide head called brachycephaly (from the Greek term *brachkus* for short). Unilateral coronal synostosis causes flattening of the ipsilateral forehead and displacement of the ipsilateral lesser wing of the sphenoid bone superolaterally called the "harlequin eye deformity" since radiographically it has the appearance of a masquerade mask. Other features include ipsilateral nasal deviation and contralateral displacement of the anterior fontanelle. This skull pattern produced by unilateral coronal synostosis is termed anterior plagiocephaly (*plagos*: Greek for slant).

Metopic synostosis is found in 20-29% of non-syndromic cases but studies have shown increasing prevalence.[24,25] Premature fusion of the metopic suture causes arrested growth of the cranium in the transverse direction anteriorly and increased anteroposterior growth. This narrowing of the frontal bone produces a pointed triangular forehead with orbital hypotelorism and a ridge along the fused metopic suture and there may be compensatory posterior growth causing widening of the parietal regions. This is called trigonocephaly (*trigonos*: Greek term for triangle). However, it is important to note that ridging not infrequently occurs with normal fusion during the first few months of life and does not require surgery.[26]

Lambdoid synostosis is rare, occurring in 0-5% of non-syndromic cases[17,20] and is usually unilateral. Due to premature fusion of one of the lambda sutures there is arrested growth of the ipsilateral occipital region causing ipsilateral occipital flattening, posteroinferior displacement of the ipsilateral ear and tilting of the skull base towards the affected suture. Compensatory growth occurs at the contralateral occipital and frontal regions resulting in contralateral forehead and occipital protuberances as well as inferior mastoid elongation. This posterior slanting shape is called posterior plagiocephaly. Bilateral lambdoid synostosis is very rare and causes symmetrical flattening of the occiput with compensatory heightening the skull. This is called posterior brachycephaly and in combination with posterior sagittal synostosis also known as the "Mercedes Benz" sign due to the changes on the X-rays.[27] Bilateral lambdoid synostosis is associated with a Chiari I abnormality (with protrusion of cerebellar tonsils through the Foramen magnum) and can appear similar to brachycephaly due to coronal synostosis.

A similar presentation, and by far the most common one, can occur in positional plagiocephaly ("moulding"), a prevalent acquired cranial asymmetry that emerges at 6 weeks of age and can largely be attributed to the supine sleeping position recommended for infant safety (in the UK generally referred to as the "Back to Sleep" campaign for the prevention of Sudden Infant Death Syndrome).[28-30]

The two can be difficult to distinguish (see Figure 2), but the ipsilateral ear is anteriorly displaced in positional plagiocephaly and skull base tilt is absent. Positional plagiocephaly is asserted to be benign and may resolve spontaneously in some cases[32,33] or with simple measures such as position changes, "tummy time" and physical therapy for any torticollis that may be present.[30,31]

Although orthotic ("moulding") helmets are frequently used (particularly in Europe and the USA),[33,34] Wijk et al. demonstrated in HEADS (HElmet therapy Assessment in Deformed Skulls), a single blinded, randomised controlled trial, that there is no benefit

Unilateral plagiocephaly
- Unilateral occipital flattening
- Anterior displacement of the ipsilateral ear
- Ipsilateral frontal bossing (bossing opposite occiput)
- Contralateral forehead flattening
- Parallelogram shape

Lambdoidal synostosis
- Ipsilateral flattening of the occipitoparietal region
- Posterior displacement of the ipsilateral ear
- Contralateral parietal/ frontal bossing
- Tilted cranial base with mastoid deformity
- 'Windswept' deformity

Bilateral plagiocephaly
- Bilateral occipital flattening
- Central posterior flattening
- Posterior skull widening
- Bitemporal bossing

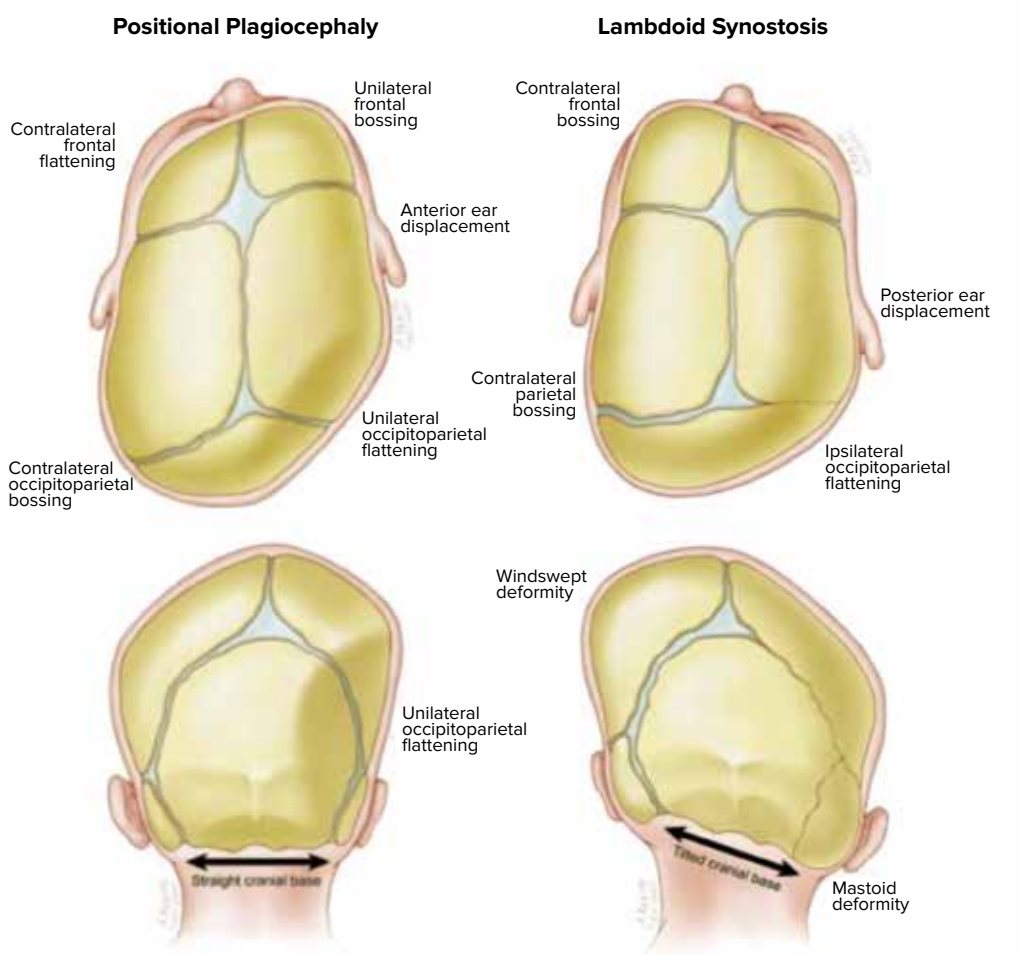

Figure 2. Positional Plagiocephaly. Adapted from International Society of Paediatric Neurosurgery (ISPN) website.[31]

from the administration of a moulding helmet and discouraged its use due to the association with large costs and prevalent side effects.[35] The overall consensus in the UK is to not recommend it.

Synostoses occur in multiple sutures in 5-15% of non-syndromic cases,[17,20] presenting with more complex deformities. Synostosis of three or more sutures is referred to as pansynostosis[36,37] and can present either with microcephaly or as a "Kleeblattschädel" (cloverleaf skull), named due to the bulging of the frontal and temporal bones giving rise to a tri-lobular shaped skull.

Genetics

Nonsyndromic craniosynostosis accounts for approximately 85% of cases[3] and although positive family histories have been reported,[38,39] the aetiology remains unknown. However, one cohort study genetic analysis found single gene mutations in *FGFR2, FGFR3, TWIST1* and *EFNB1* in 11 out of 204 (5.4%) of non-syndromic cases, 9/11 of which were unilateral or bilateral coronal.[40]

Other factors, including increased thyroid hormone level during pregnancy, and environmental stimuli such as head compression *in utero*, maternal smoking and teratogenic medications have also been implicated.[41] Of particular note is the association between maternal use of sodium valproate and metopic craniosynostosis.[42] On the other hand, most types of syndromic craniosynostoses are inherited in an autosomal dominant fashion[43,44] and genetic analysis studies have provided strong links to a number of genes.[43]

One such group of genes implicated is the fibroblast growth factor receptor family, of which mutations in genes encoding *FGFR1*, *FGFR2* and *FGFR3* have been found in syndromic craniosynostoses. These are receptor tyrosine kinases that undergo auto-phosphorylation upon fibroblast growth factor binding and are involved in a vast range of cell functions and developmental processes.[45,46] Indeed, targeted mutagenesis of individual *FGFR* isotypes has been shown to lead to both lethal or viable defects in embryological development such as gastrulation,[45] placenta and limb bud formation,[47,48] organogenesis[49] and bone ossification.[50]

FGFR mutation results in gain of function causing abundant activation of the *FGF/FGFR* signalling pathway, which is then leading to expression of runt-related transcription-factor 2 (*RUNX2*). The result is early onset differentiation of mesenchyme cells into osteoblasts that deposit bone and eventually lead to premature suture closure.[51,52] *FGFR1* mutations have been identified in Pfeiffer and Jackson Weiss syndromes; *FGFR2* mutations in Crouzon, Jackson Weiss, Apert, Pfeiffer and Beare Stevenson syndrome; and *FGFR3* mutations in Crouzon syndrome with Acanthosis, Muenke syndrome and Thantophoric dysplasia (see Table 1 and Figure 3). The mechanism resulting in significantly differing phenotypes arising from the same mutation is yet to be fully understood.

TWIST1 (twist-related protein 1) is another gene linked to craniosynostosis syndromes and mutations have been found in the Saethre-Chotzen syndrome. *TWIST1* is a basic loop-helix-loop transcription factor and thought to be involved in determining the lineage of osteoblasts. Cells over-expressing *TWIST1* showed decreased response to *FGF* and remained undifferentiated while cells under-expressing *TWIST1* differentiated into a mature osteoblast-like state.[53]

Therefore, it has been hypothesised that *TWIST1* is involved with delaying suture fusion, upstream of *FGF*. Indeed, the majority of *TWIST1* mutations found in Saethre-Chotzen syndrome confer a loss of function through haplo-insufficiency.[54] Furthermore, *FGFR2* and *FGFR3* mutations have also been found in Saethre-Chotzen syndrome[55] further supporting a common molecular pathway.

Table 1. Genetic mutations and their craniofacial phenotype.
Adapted from Senarath-Yapa et al., 2012 and Flaherty et al., 2016. The phenotypic features described may not be present in all individuals diagnosed with the condition. According to Wilkie et al., 2010, Muenke syndrome is clinically not diagnostic as phenotypic appearances vary from no characteristics to overlapping with other craniosynostosis syndromes.

Gene Chromosome	Syndrome Characteristic phenotype	Hydrocephalus?
FGFR1 8p	**Pfeiffer syndrome** Premature suture closure, brachycephaly, cutaneous syndactyly, hypertelorism, high forehead, midfacial retrusion, beaked nose, hearing loss, dental problems, brachydactyly, digit webbing, syndactyly, cloverleaf skull deformity, developmental delay, cognitive deficits	Yes (>90%)
	Jackson Weiss syndrome	
FGFR2 10q	**Crouzon syndrome** Premature suture closure, brachycephaly, flat forehead, midfacial retrusion, eye proptosis, hypertelorism, mandibular prognathism, beaked nose, mild limb abnormalities, variable cognitive function	Yes (>90%) Chiari I
	Jackson Weiss syndrome	
	Apert syndrome Premature suture closure, brachycephaly, eye proptosis, midfacial retrusion, exorbitism, hypertelorism, heterotropia, high arched palate, cleft palate, structural brain anomalies, cognitive impairment, complex syndactyly	Yes (~70%)
	Pfeiffer syndrome	Yes
	Beare Stevenson syndrome	
FGFR3 4p	**Crouzon syndrome** with Acanthosis Premature suture closure, brachycephaly, midfacial retrusion, acanthosis nigricans	
	Muenke syndrome Premature suture closure brachycephaly, orbital hypertelorism, midfacial retrusion, high arched palate, hearing loss, mild anomalies of the hands and feet, developmental delay	Yes (Seldom)
	Thantophoric Dysplasia	
EFNB1 Xq	**Craniofrontonasal syndrome**	Seldom
TWIST1 7p	**Saethre-Chotzen syndrome** Premature suture fusion, brachycephaly, high forehead, low frontal hairline, ptosis, hypertelorism, broad nasal bridge	Yes (30-50%)

More recently, Zhao et al., 2015 discovered that *Gli1+* cells in the suture mesenchyme form the osteogenic front, periosteum, dura and all craniofacial bones, and are involved in injury repair.[56] Ablation of *Gli1+* cells in mice was found to cause pansynostosis, arresting of skull growth and reduced injury repair. Moreover, the *Gli1+* population was reduced in *Twist1*$^{+/-}$ mice, a widely used model of craniosynostosis mimicking the *TWIST1* mutation in Saethre-Chotzen syndrome, and causing increased mesenchyme apoptosis and reduced proliferation. Therefore, the authors showed that *Gli1+* cells in the suture mesenchyme form the osteogenic stem cells of the craniofacial sutures and that pathogenesis of craniosynostosis may be due to reduced numbers of *Gli1+* cells.

Associated complications

Each type of craniosynostosis can vary in its severity of phenotypic features. In particular, sagittal and metopic suture synostosis may show a very mild clinical presentation in which only one bone ridge at the afflicted suture is visible and/or palpable. Therefore, parents are often confronted with health care professionals who do not recognise the craniosynostosis in a timely manner shortly after childbirth. This may not only cause distress for the parents but also lead to delayed diagnosis and treatment.[64] In syndromic and complex nonsyndromic craniosynostoses the patients may suffer from cognitive impairment and raised intracranial pressure (ICP). Several syndromic craniosynostoses are associated with skeletal hypoplasia of the midface resulting in a narrowed airway. In approximately 50% of cases this leads to OSAS (obstructive sleep apnoea syndrome). Other risks and complications include cornea injury due to exorbitism, malocclusion and

Figure 3. Most common craniosynostosis syndromes.

Crouzon syndrome,[57] first described by Octave Crouzon in 1935, is the most common of the craniosynostosis syndromes, occurring in 1 in 25,000 live births. Like the majority of the syndromes including Apert, Pfeiffer and Saethre-Chotzen, it follows an autosomal dominant inheritance pattern[7] and mutations have been found in *FGFR2* and *FGFR3*. Most commonly affected are the bilateral coronal sutures causing brachycephaly. Also seen is hypertelorism, shallow orbits resulting in exophthalmos, maxillary hypoplasia causing mandibular prognathism, high arched palate and low set ears associated with hearing impairment. Crouzon syndrome is also thought to convey an increased risk of raised intracranial pressure[58] and this has been proposed to be due to the early closure of the sagittal and lambdoid sutures.[59] As a result cognitive function in individuals with Crouzon syndrome is variable. Additionally, this syndrome may well be progressive in the first 2-3 years of life and even within the same family can have quite marked differences in phenotype.

Apert syndrome is the second most common, found in 1 in 100,000 newborns, the majority of which are sporadic mutations in *FGFR2*. It also affects the coronal sutures bilaterally causing a brachycephaly[60] with hypertelorism, shallow orbits, exophthalmos and high arched palate. However, maxillary hypoplasia is more severe than observed in Crouzon syndrome and can lead to life-threatening airway compromise. Also seen is an anterior open bite, downslanting palpebral fissures, a "parrot beak" nose and syndactyly of the second, third and fourth digits.

Pfeiffer syndrome also occurs in 1 in 100,000 live births, most commonly due to *FGFR2* mutations, but *FGFR1* mutations have been found in 5% of cases, causing a less severe presentation.[61] The coronal, lambdoid and sagittal sutures are all affected, but heterogeneity of the syndrome has led to a classification into three clinical types. Type I is the classic, most common and least severe type associated with turribrachycephaly, hypertelorism, strabismus, maxillary hypoplasia causing mandibular prognathism and characteristic broad thumbs. Type II is more severe, with a cloverleaf skull, severe exophthalmos, hydrocephalus and poor prognosis. Type III is very similar to type II but lacks the cloverleaf skull.[62]

Saethre-Chotzen is found in 1 in 25,000 to 50,000 newborns and caused by mutations in *TWIST1*. The phenotype is heterogenous and synostosis can be bicoronal, unicoronal, sagittal, metopic or multisutural[63] leading to a great variety of head shapes. Other features include a low hairline, ptosis, facial asymmetry and ear deformities. Additionally, syndactyly of the second and third digits may be present. Overall, Saethre-Chotzen syndrome perhaps displays the widest phenotype of the common syndromic conditions and family members may remain undiagnosed due to portraying mild phenotypic features (e.g. subtle ptosis).

aesthetic/psychosocial problems. Associated intracranial abnormalities in syndromic craniosynostoses are increased ICP, Chiari I malformation, ventriculomegaly and hydrocephalus. Hearing loss is described for all types of syndromic craniosynostoses. Visual pathologies such as astigmatism and strabismus are very frequent in syndromic craniosynostoses. In nonsyndromic craniosynostosis, specifically unicoronal craniosynostosis, children are at risk of developing astigmatism in the eye opposed to the coronal suture synostosis.[65] Limb deformities are largely restricted to syndromic craniosynostoses, and notably associated to the Apert syndrome. Both types of craniosynostosis, nonsyndromic and syndromic, may co-occur with cognitive and behavioural impairments. These are either intrinsic due to the congenital defect or secondary to intracranial hypertension or physical deformities. Interestingly, there is continued debate on decreased intracranial volumes, hydrocephalus and raised ICP in patients with single-suture craniosynostosis.[27] So far, there is little to no difference in intracranial volumes among various types of craniosynostoses to be found.[66,67] Similarly, there was no correlation between hydrocephalus and nonsyndromic craniosynostosis established,[68] unless there is bilateral involvement of the lambdoid suture.

However, several studies have shown that children with nonsyndromic craniosynostosis are at high risk of developing intracranial hypertension.[58] In fact, elevated intracranial pressure was found in 24-30% of nonsyndromic craniosynostoses.[6,69] Yet in 1982, Renier et al.[6] reported abnormal ICP recordings (meaning ≥15mmHg during Slow-Wave sleep) in 14% of cases where only one suture is involved and in 47% of cases with multiple sutures intricated. However, in most nonsyndromic cases indication for surgery remains cosmetic. Invasive ICP monitoring is reserved for children with visual and/or developmental deficits, in cases where surgery has been refused and the head circumference is falling off or they have a "Copper beaten skull" on X-ray - although this is a weak clinical sign.

Apart from its association with intracranial hypertension, premature fusion of cranial sutures is also known to affect the underlying brain morphology. In a series of studies, conducted by Aldridge et al. from 2002 to 2005, the authors demonstrated that both cortical and subcortical structures of the central nervous system are dysmorphic in craniosynostosis. Specifically, studies of brain morphology in cases of sagittal and unicoronal synostosis have demonstrated that changes in the brain's structure are found in adjacent as well as distant and in subcortical regions away from the fused suture.[70-72]

The highest percentage of associated intra- and extracranial midline problems can be found in children with metopic synostosis. These patients also most commonly present with an IQ deficit. Birth weight, parental age and sodium valproate use during pregnancy have been identified as potential risk factors for the development of metopic craniosynostosis.[42,73]

Hydrocephalus and tonsillar descent (Chiari I malformation) merit a specific discussion. Chiari I (for the purpose of this article refers to tonsillar descent and crowding of the foramen magnum) has a clear association with the syndromic craniosynostoses shown in Figure 3. An association between non-syndromic lambdoid synostosis (and not other sutures) and Chiari I has also been noted.[74] Chiari I and craniosynostosis co-existing have a significant association with syringomyelia,[74] which needs to be taken into account when evaluating and imaging these children. One of the hypotheses for the aetiology of Chiari malformation is the "box being too small for the contents" due to occipital hypoplasia. Craniosynostosis, whilst obviously not due to occipital hypoplasia, results in the net same outcome of the skull being disproportionately too small for the brain. This provides a plausible mechanism for the association between Chiari and craniosynostosis as well as potentially giving greater insights into the pathogenesis of Chiari malformation itself.

Hydrocephalus associated with craniosynostosis is common. There is variation in the reported figures for hydrocephalus across the literature, but overall syndromic craniosynostosis is associated with hydrocephalus in up to 30-70% of cases,[68,75] as opposed to nonsyndromic craniosynostoses where it occurs in less than 2%. Furthermore, there is no evidence to suggest any causality between the two in most cases of nonsyndromic synostosis.[76]

The first and key point is to establish whether one is dealing with genuine hydrocephalus or static ventriculomegaly with no increased pressure. This is not always a straightforward task as the synostosis itself may cause raised ICP and the clinical picture is complex, head circumference is not possible to use and radiological signs may be atypical.

The mechanism of hydrocephalus in craniosynostosis is believed to be a mixture of obstructive and absorptive[77] arising from venous hypertension.[78] Brain atrophy may contribute to static ventriculomegaly, producing a "hydrocephalus ex vacuo" picture.[76] Although not the focus of this article, the existence of acquired craniosynostosis secondary to shunt over drainage in the presence of non-fused sutures should be mentioned as well.

- Cranial growth restriction/ physical deformity
- Raised ICP
- Cognitive impairment

Multidisciplinary team

With regard to the number of complications that can arise intra- and post-operatively from open cranial vault procedures the multidisciplinary team concept has developed and is widely used. It is largely based around protocols for workup, delivery of anaesthesia, streamlined surgical procedures and complex post-operative care and assessment.[79]

The involved specialties usually include Plastic Surgery, Neurosurgery, Otolaryngology, Dentistry, Audiology, Ophthalmology, Speech & Language therapy, Developmental Paediatrics, Neuropsychology, Medical Genetics, Social Work and Nursing Care. Other specialists, such as cardiologists and gastroenterologists, may be consulted for management of associated defects and clearance for surgery. Often parents can easily be overwhelmed by all the information discussed when meeting all the different specialists. Moreover, congenital defects involving a child's face and skull seem to evoke particularly strong emotional responses from the parents, who must contend with a host of potentially stressful events and circumstances, including the infant's unusual physical appearance, the perspective of potentially life-threatening surgeries ahead, and the possibility of future neuropsychological and educational problems.[4]

Diagnosis

In order to achieve optimal treatment and satisfactory surgical outcome,[80] early diagnosis is essential in children with craniosynostosis. However, patients are not infrequently referred late or not referred at all due to late recognition of the head shape deformity.[64]

Usually the abnormal skull shape is recognised shortly after birth by either the parents themselves, the treating obstetrician or paediatrician, midwife or general practitioner. The main diagnostic screening tools are physical examination of the skull shape[80,81] in combination with taking the history.[82,83] The anamnestic flowchart of Bredero may serve as a guideline to distinguish craniosynostosis from positional skull deformities.[84] When craniosynostosis is suspected, the paediatrician should refer the child to a craniofacial centre for further diagnostic investigations. X-rays of the skull (A-P, lateral, Towne's view) are still often performed in cases of suspected craniosynostosis. If the result remains uncertain, the X-ray may be repeated after 1 to 2 months. Alternatively, an experienced investigator can perform ultrasound scanning of the cranial sutures.

CT-scan with 3D-reconstruction is performed as an alternative in some centres.[64] Whilst the imaging will also give some detail relating to the brain (hydrocephalus, etc.) it is associated with significantly more radiation and not necessarily of added value in many/most cases of "simple" craniosynostosis.[85] Image findings may include bony ridging along the suture, heaping up of bone at the suture, sutural narrowing, and indistinctness of the suture as primary signs of craniosynostosis.[86] Secondary signs include an altered calvarial shape, the general changes in shape and timing of closure of fontanels, and other facial anomalies. The lack of growth across a suture commonly results in effacement of the

underlying subarachnoid spaces. Patients with craniosynostosis may also have an enlarged subarachnoid space beneath regions of compensatory skull growth.[87]

In summary, the diagnosis of craniosynostosis is based on the calvarial shape with relation to a calvarial suture. Nonsyndromic craniosynostosis is diagnosed mainly clinically with help of X-rays and CT scans performed in some centres. In contrast to that, syndromic craniosynostosis is often more complex and often requires both CT and MRI imaging to look at the structures within the posterior fossa and venous drainage. For both syndromic and non-syndromic craniosynostosis other investigations should include: regular measurement of the head circumference (and the Cranial Index - width/length), ophthalmology, ENT, neurocognitive, Speech & Language assessments, and where appropriate dental review, measurement of overnight Oxygen saturations (to exclude sleep apnoeas associated with airway problems) and Plastic Surgery opinion for hand and feet abnormalities.

Genetic testing and counselling can assist in making or confirming a specific diagnosis and this may have prognostic implications both for the individual patient but also for future planned pregnancies.[64]

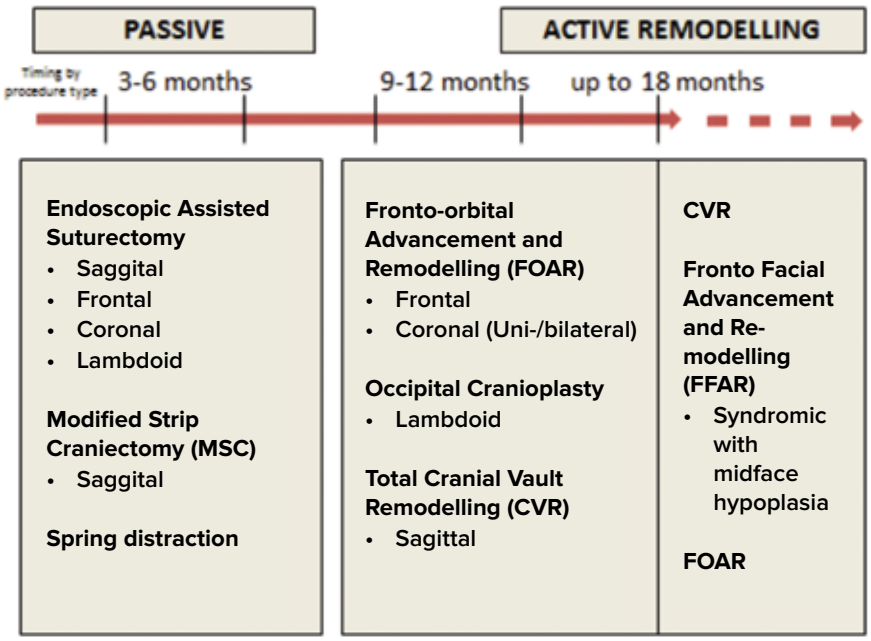

Figure 4. Overview on operative techniques for simple craniosynostosis. Early surgery allows for brain growth to passively reshape skull. Later surgery aims to actively remodel skull shape. The time bar reflects procedure type in broad terms.

- Physical examination and history taking
- Diagnostic imaging: X-skull/ ultrasound, 3D-CT scan of the head
- Genetic testing

Neuropsychological outcomes

In syndromic cases surgery is often indicated for morphological (aesthetic) and functional (cognitive, airway, ophthalmic, etc.) reasons. However, in non-syndromic cases, the indication for surgery is still generally considered to be cosmetic. Although, recent evidence suggests that corrective surgery may also positively impact developmental outcomes assessed during long term follow up in non-syndromic synostoses.[88]

Many of the older studies looking at cognitive outcomes poorly defined mental retardation, lacked control subjects, adequate follow-up periods and valid, standardised psychometric tests. On the other hand, more recent, high quality studies applying the above mentioned principles including formal assessments, such as the Bayley Scales of Infant Development and Wechsler Intelligence Scales for Children, have raised the possibility of mild cognitive impairment even in non-syndromic cases. A systematic review by Knight et al., 2014[89] of 33 articles with particular emphasis on methodological quality found 10 studies showing developmental delays in motor functioning and cognition, including language, both before and after surgery. Five studies of school-age children with single suture craniosynostosis found Intellectual Quotient to be within the normal range, but three studies found increased learning, behavioural and language deficits documented on medical records or reported by parents, and five studies showed greater speech and language impairment by more formal testing. A few studies uncovered impairment in visual spatial skills, memory and attention, and school performance. Knight at al., 2014 also investigated the literature on correlations between neurodevelopmental outcome and a variety of factors: no articles to date have significantly correlated neurodevelopmental outcomes and brain imaging, severity of deformity, sutures affected, genetics or gender. Interestingly, there is mixed evidence for the association between early surgery and the reduction of neurodevelopmental impairments, with some studies reporting better outcomes with surgery within one year of age and worse outcomes with delayed surgery after four years;[90] other studies have reported no such difference.[91-93]

In addition to cognitive difficulties, psychosocial aspects of craniosynostosis have been investigated. Clearly during early years of infanthood, the major psychosocial burden lies with the parents and this is reflected in the need for parental support. Particularly, parents of a child with syndromic craniosynostosis may have to cope with negative reactions from others, a possible discrepancy between deviating physical appearance and cognition, and be confronted with problems of school choice.[64] Once the child grows older and attends school, they may be themselves presented with psychosocial challenges and management of these should in turn focus on the child. A variety of outcomes such as post-traumatic stress, successful completion of treatment and the child's resilience and coping strategies have been linked to parental factors such as support as well as the parents' own coping ability.[94]

Post-traumatic stress disorder (PTSD) is an important issue in all children heavily engaged in the healthcare system and relates to iatrogenic factors such as handling by multiple different clinicians, experiencing pain, separation from parents and undergoing procedures (e.g. phlebotomy, imaging) against the infant's will, with severe developmental and psychosocial implications later in life. Indeed, 10% of children admitted to an intensive care unit were found to develop PTSD, with parental stress reactions as the strongest correlated predictor,[95] highlighting again the importance of addressing psychosocial issues within the whole family. Unsurprisingly, psychosocial outcomes relating to self-image and resilience are also influenced by parental response and resilience.[94]

Evidence on behavioural problems has been mixed: using the Child Behaviour Checklist, Becker at al., 2005 reported significant differences between children with craniosynostosis and the general population;[96] whereas Van der Vlugt et al., 2009 found no difference to the general population when accounting for IQ.[97] At school age, Kelleher et al., 2006 found that in children with nonsyndromic trigonocephaly, 33% required assessment by a school psychologist; 47% required remedial or resource hours; 20% required a special needs classroom due to behaviour issues; and 37% were reported to have behavioural issues such as attention deficit disorder, autism and hyperactivity by their parents.[98]

In later school life and adolescence, issues pertain to stigma and bullying, with a third of craniosynostosis patients experiencing this.[64] Most cope sufficiently but continued support is important, with social skills interventions proving beneficial.[99] Another issue arising in adolescent patients is autonomy to make decisions relating to treatment as they reach the age required for consent: it is of vital import-

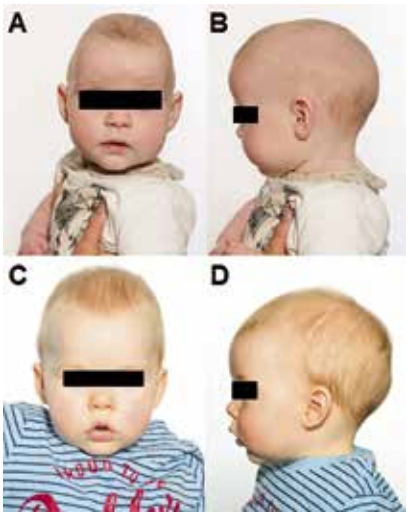

Figure 5: Sagittal craniosynostosis
A and B: pre-operative photograph of a child with sagittal craniosynostosis (A frontal view, B lateral view) resulting in a "long-boat" shaped skull; C and D: post-operative photographs (C frontal view, D lateral view) after treatment with spring distractors.

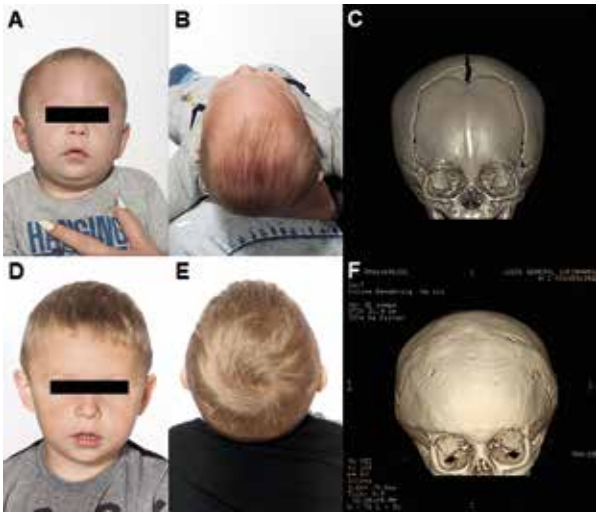

Figure 6: Metopic craniosynostosis
A and B: pre-operative photograph of a child with metopic craniosyonostosis (A frontal view, B top view) resulting in a triangular headshape; C: pre-operative CT 3D Reconstruction demonstrating premature fusion of the metopic suture; D and E: post-operative photograph after treatment (D frontal view, E top view); F: post-operative CT 3D Reconstruction.

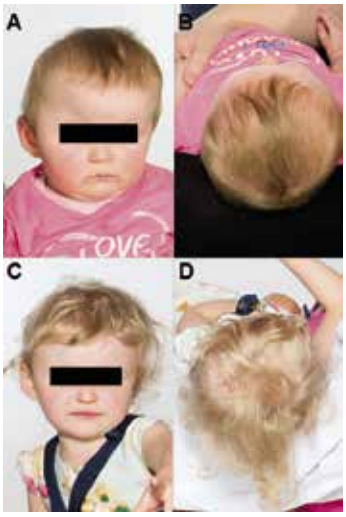

Figure 7: Unilateral unicoronal craniosynostosis
A and B: pre-operative photographs (A frontal view, B top view) of a child with right unicoronal craniosynostosis resulting in flattening of the ipsilateral forehead and displacement of the ipsilateral lesser wing of the sphenoid bone superolaterally; C and D: post-operative photographs after treatment (C frontal view, D top view).

ance for them to be involved in the decision-making process in order to optimise their cooperation and satisfaction.[100] Furthermore, it is critical that adolescents have realistic expectations of treatment.

Although there have been no studies following up nonsyndromic craniosynostosis patients for psychosocial problems in adulthood, some have identified psychosocial problems in adults with syndromic craniosynostosis. Relative to controls, adults with Apert and Crouzon syndromes had a lower level of education, were less often married, experienced less sexual relationships and more commonly had periods of depressive mood, but were as likely to report a positive attitude to life as controls.[101,102] Some adults with non-surgically treated craniosynostosis reported such pronounced psychological problems that they were willing to undergo correction in adulthood, a fundamentally more complicated operation than in infants.[103]

Treatment

The surgical treatment of patients with syndromic craniosynostosis was developed in Paris in the early 1970s by Tessier[104] and then later by Marchac and Renier.[105] Surgery had a 2-fold aim: to achieve an enlargement of the cranial volume so as to prevent sequelae of ICP (e.g. developmental delay, visual impairment, etc.), and the correction of morphologic abnormalities of the cranium, the orbits, and the upper jaw.

Since the first surgical intervention for craniosynostosis, a great many surgical techniques for the various types of craniosynostosis have been described and it must be emphasized that there is no consensus on the optimal surgical techniques for skull reconstruction in any form of craniosynostosis.[26]

However, a broad distinction can be made between "passive" techniques and "active" remodelling procedures (see Figure 4). Passive methods involve resection of bone, thereby allowing the developing and expanding brain to modify the skull shape (with or without assistance of a moulding helmet). As can be seen from a standard head circumference chart the first few months of life are associated with the greatest rate of skull growth (due to rapid brain growth) – most skull growth occurring in the first 2 years of life. More recently, these passive techniques have been further refined by minimally invasive techniques which are associated with smaller skin incisions and the need for less blood transfusions.[9] Such techniques include endoscopic strip craniectomy (+/- moulding helmet) as pioneered by Jimenez[106,107] or the use of spring distraction.[108-115]

The active remodelling techniques, on the other hand, do not rely on the self-correcting capability, but attempt to obtain the desired skull shape by direct reconstruction (often utilising rigid fixation using absorbable plates and screw).[64] This type of surgery can also be broadly divided into that used to correct sagittal synostosis[116] (Figure 5) and that used to treat metopic (Figure 6) and coronal synostosis (Figure 7) – which usually involves a fronto-orbital advancement and remodelling (FOAR). This latter procedure requires the orbital bar to also be removed as well as the abnormal area of the front of the skull.

It has to be considered that in contrast to open craniosynostosis correction surgeries, which are generally performed between the ages of 6 to 18 months, minimally invasive procedures are performed much earlier within the first 3-6 months of age requiring early diagnosis and referral.[117,118]

However, the best surgical treatment has to be evaluated by the surgeon for each individual. Furthermore, especially in more complex syndromic craniosynostosis more than one surgery may be required.

a. Early intervention: Endoscopic or open strip craniectomy or spring distraction +/- post-operative orthotic helmet

vs.

b. Later intervention: Open calvarial reconstruction

Conclusions

The identification of the underlying genetic mutations and molecular mechanisms in craniosynostoses has led to a breakthrough in our understanding of these pathologies. A variety of procedures may be used to correct the deformity but over recent decades there has been increasing interest in early minimally invasive interventions where possible. Therefore, early diagnosis of craniosynostosis is imperative.

A multidisciplinary team approach in children with craniosynostosis and offering support to the entire family, including the parents, remains a vital factor in management of children with these pathologies. Long-term follow-up is particularly important as these children may encounter various problems throughout different stages in their development, including school age, adolescence and even further into early adulthood. Also, arising cognitive difficulties in non-syndromic craniosynostoses may be very subtle.[119] Consequently, children will benefit from continuous assessments throughout childhood and early adulthood and in this way neuropsychological issues can be discussed and addressed accordingly.

References: A full list of references can be found online at www.acnr.co.uk

Huntington disease: from premanifest to diagnosis and early care

Elizabeth A McCusker
MBBS (Hons) FRACP, is a Senior Staff Specialist in the Neurology Dept. of Sydney's Westmead Hospital and Clinical Associate Professor, Sydney Medical School, Sydney University. Involved with Huntington Disease care and clinical research for 30 years, she established and was Director of a comprehensive service of HD care that includes predictive testing, clinical research and service with multidisciplinary outreach and an inpatient assessment and chronic care unit. Dr McCusker has participated in many of the multisite International research initiatives of observational and treatment trials, that include the Huntington Study Group, PREDICT HD, COHORT, 2-CARE, and ENROLL HD. She has a particular interest in care provision in neurodegenerative disease and the ethical challenges encountered in inherited disease with cognitive impairment.

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Images demonstrating progressive striatal atrophy from the Predict HD study with kind permission of Dr Jane Paulsen, Principal Investigator, University of Iowa USA.

Correspondence to:
elizabeth.mccusker@sydney.edu.au

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Abstract
Huntington disease (HD) has a prolonged premanifest phase. Detailed premanifest HD studies followed identification of the causal CAG repeat expansion in the Huntingtin gene in 1993 that allowed genetic testing. Better understanding of the years before clinical diagnosis and variation in disease presentations, resulted. Information from these premanifest studies and new biomarkers may enable a wider definition of HD, earlier diagnosis and care, as well as better measures of progression in clinical trials.

Manifest HD
Manifest Huntington disease diagnosis relies currently on the presence of motor signs on examination. Typical choreiform movements remain the disease hallmark. Cognitive and behavioural features may predominate.[1] HD is a dementing illness with a phase equivalent to the mild cognitive impairment (MCI) described in other dementias.[2] With a prevalence of up to 12.28/100,000 and higher in some Western populations, HD is the commonest cause of dementia in younger people.[3]

Assessments
A detailed history, from the person and a companion is important to determine the full extent of the disease features, family history, social support network, level of function and impact on the person and those around them.

The Unified Huntington Disease Rating Scale (UHDRS) documents cognitive, behavioural, motor and functional manifestations. This validated scale is used in most HD observational and drug trials. A diagnosis is made based on the DCL (diagnostic confidence level) rated 0-4, with a score of 4 equating to a > 99% certainty that the motor findings are due to HD. There is some subjectivity to this decision made after the motor examination, documented as the UHDRS total motor score (TMS). This scale scores the eye movement disorder, speech, finger taps, tandem gait, chorea and other motor features.[4] Cognitive testing is essential at presentation. The Montreal Cognitive Assessment is preferred over the MMSE. Dysphagia, weight loss, impulsiveness and unawareness, although prominent, are not directly included in the UHDRS.[1]

Presentations of manifest HD and the Variable phenotype
Patients who present to the clinic, especially with an unknown family history or a phenotypic variation, may have well-established disease.

Disease features of cognitive impairment and unawareness contribute to presentations later in the disease course.[5]

Younger onset (Juvenile) with a longer repeat expansion,[6] late onset,[7] and those with predominantly cognitive and behavioural manifestations, occur.[8] The main reason for the different ages of onset is variation in the length of the CAG repeat expansion within the HTT gene.[1] The longer the repeat, the earlier the onset. Variations in onset age and features, even with the same repeat length, are postulated to be due to environmental and genetic modifiers.[9]

The contribution of Premanifest studies
HD is a disease with a single genetic cause with established genetic testing programmes for 25 years. A number of premanifest studies of mutation carriers have contributed to our knowledge of this phase of the condition. Amongst the most detailed are the PREDICT-HD study of over 1000 individuals with the repeat expansion that ran over 10 years,[10] the PHAROS study[11] of 983 untested individuals 'at risk' because of family history and the TRACK HD study.[12] In addition, large longitudinal observational studies including COHORT, Registry and the current ENROLL study, added even more details about the premanifest path to clinical diagnosis and progression.[1,9]

The major finding from these studies is that subtle but progressive changes in neuroimaging findings, particularly striatal volumes, cognition, behaviour and motor examination occur during the premanifest phase and progress over the years before a definite clinical diagnosis. These findings are sufficient to define a prodromal phase closer i.e. within five years, of clinical onset.

With more experience of this crossover from premanifest to definite disease, the diagnosis can be made earlier than previously. Although changes occur in domains other than motor, most would not be confident to make a diagnosis of HD based on behavioural and cognitive features alone.

Research diagnosis
As in other dementias, most notably Alzheimer's disease, a clinical diagnosis is separated from the research diagnosis.

Genetic testing for the CAG expansion is available to those aged 18 years and over. Many know of their carrier status for a long period before their eventual disease onset and perhaps witnessed it in their affected relatives.

These premanifest individuals usually present earlier for clinical diagnosis. Some seek reassurance that overt disease is not yet evident. Some decide on testing and then prefer no service contact and to live life as normal until affected, often significantly. A greater proportion of unaffected people with a family history, decide not to have a premanifest genetic test.

Predictions of onset have been extrapolated from the CAG repeat lengths. It is not possible to determine age of onset accurately for an individual based on the CAG repeat length. It is however possible to tell an 18

year old with a repeat length of 40 that they will not be affected for some years i.e. 10 or more likely 20 years.

Progressive atrophy notably in the striatum, corpus callosum, insular in particular are documented on a range of imaging modalities in the premanifest phase before overt signs of disease.[10,12]

Measurement of Huntingtin protein in the CSF and blood and more recently in saliva is possible.

Manifest disease would not be diagnosed in the clinic based on these earliest changes, although these components are valuable in research studies, if standardised and reproducible as possible biomarkers of progression.

What are the premanifest and clinical findings that assist in diagnosis?

On a recent review of data from HD studies, TMS, Total Functional Capacity (TFC), Symbol Digit Modality and Stroop Word Reading are considered the most reliable items to support the clinical diagnosis in this earliest stage of premanifest to manifest diagnosis. As a result, Schobel et al propose a composite UHDRS.[13]

Why a diagnosis?

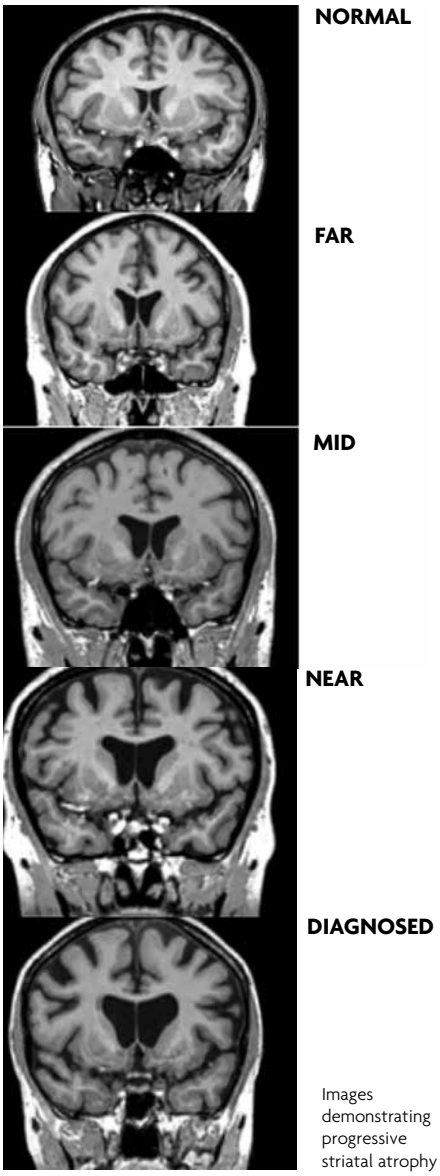
With genetic testing, protocols became available to assist in ensuring fully informed consent before testing premanifest, unaffected people. The process of testing, the reaction to results and confidentiality and discrimination concerns are emphasised. Diagnostic testing for people with a suspected clinical diagnosis of HD is a confirmatory test. An explanation of the implications of a positive test in this situation should be undertaken and where possible consent of the person or a person responsible is required.

There is no cure. Although there are recent promising advances in genetic therapies[14] that target the expanded repeat, a cure is some years ahead.

The premanifest group, often years away from clinical onset, face uncertainty about the time of definite diagnosis. The task of deciding whether symptoms and signs in these people constitute a clinical diagnosis and when to disclose a definite diagnosis can be difficult.[15] Many manifestations found in the premanifest study participants, occur in the unaffected population e.g. depression, apathy and irritability. In addition unawareness of disease onset is prominent in HD including at an early stage. Sometimes this is because the signs visible on examination do not produce any functional impact i.e. the eye movement disorder of slow pursuit and saccades. Very obvious chorea may not be noticed and along with the behavioural changes are often more apparent to a companion. Studies show that the divergent reports of symptoms and signs between the person, their companion and the examiner, are consistent with unawareness.[5]

It could be argued that if the person is unaware of manifestations and there is no functional impact, then why make an earlier diagnosis? This raises many valid ethical considerations, not the least being the person's right to know.

It is important that disclosure of a changed status from premanifest to manifest is undertaken with care and based on a reliable, accurate history and reproducible signs and after assessing available support systems.



Images demonstrating progressive striatal atrophy

Beyond diagnosis

At any time, but including when premanifest "conversion" to manifest HD is disclosed, more is required than 'just a diagnosis'. An early follow up, ideally to an easily accessible, knowledgeable service with multidisciplinary care, should be offered. Ongoing contact with a general practitioner for extra support and to maintain good general health is advised and hopeful but realistic discussion of research advances.

As with other diseases of the nervous system, a healthy brain/life style intervention is recommended and cognitive and physical activity. Limiting other factors that affect the brain, i.e. alcohol and drug abuse and smoking is important as well as managing co-morbidities, including hypertension, diabetes and hypercholesterolaemia. The cognitive/behavioural and psychiatric manifestations may be prominent.[16] Many are treatable. Emphasis on review for these features is recommended and early intervention.

Preparation for the future should be advised but the slow course emphasised. HD runs a course of up to 20 years with considerable variation. Patient and carer education about manifestations, including unawareness and the other non-motor manifestations and support from disease societies and initiatives helps.

Today's premanifest generations have a reasonable expectation that their outcome and course will differ significantly from that of their affected family members.

REFERENCES

1. Ghosh R, Tabrizi SJ. *Huntington disease.* Handb Clin Neurol. 2018;147:255-278.
2. Sachdev PS, Blacker D, Blazer DG et al. *Classifying neurocognitive disorders: the DSM-5 approach.* Nat Rev Neurol. 2014 Nov;10(11):634-42.
3. Rawlins MD, Wexler NS, Wexler AR, Tabrizi SJ et al.*The Prevalence of Huntington's Disease.* Neuroepidemiology. 2016;46(2):144-53.
4. *Unified Huntington's Disease Rating Scale: reliability and consistency.* Huntington Study Group. Mov Disord. 1996 Mar;11(2):136-42.
5. Sitek EJ, Thompson JC, Craufurd D, Snowden JS. *Unawareness of deficits in Huntington's disease.* J Huntingtons Dis. 2014;3(2):125-35.
6. Moser AD, Epping E, Espe-Pfeifer P, Martin E et al. *A survey-based study identifies common but unrecognized symptoms in a large series of juvenile Huntington's disease.* Neurodegener Dis Manag. 2017 Oct;7(5):307-315.
7. Chaganti SS, McCusker EA, Loy CT. *What do we know about Late Onset Huntington's Disease?* J Huntingtons Dis. 2017;6(2):95-103.
8. Paulsen JS, Long JD. *Onset of Huntington's disease: can it be purely cognitive?* Mov Disord. 2014 Sep 15;29(11):1342-50.
9. Lee JM, Ramos EM, Lee JH, Gillis T et al and Paulsen JS; PREDICT-HD study of the Huntington Study Group (HSG), Landwehrmeyer GB; REGISTRY study of the European Huntington's Disease Network, Myers RH; HD-MAPS Study Group, MacDonald ME, Gusella JF; COHORT study of the HSG. *CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion.* Neurology. 2012 Mar 6;78(10):690-5.
10. Paulsen JS, Long JD, Ross CA, Harrington DL et al and PREDICT-HD Investigators and Coordinators of the Huntington Study Group. *Prediction of manifest Huntington's disease with clinical and imaging measures: a prospective observational study.* Lancet Neurol. 2014 Dec;13(12):1193-201.
11. Huntington Study Group PHAROS Investigators, Biglan KM, Shoulson I, Kieburtz K, Oakes D et al *Clinical-Genetic Associations in the Prospective Huntington at Risk Observational Study (PHAROS): Implications for Clinical Trials.* JAMA Neurol. 2016 Jan;73(1):102-10.
12. Tabrizi SJ, Scahill RI, Owen G, Durr A et al and TRACK-HD Investigators. *Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data.* Lancet Neurol. 2013 Jul;12(7):637-49.
13. Schobel SA, Palermo G, Auinger P, Long JD et al and TRACK-HD, COHORT, CARE-HD, and 2CARE Huntington Study Group Investigators. *Motor, cognitive, and functional declines contribute to a single progressive factor in early HD.* Neurology. 2017 Dec 12;89(24):2495-2502.
14. Wild EJ, Tabrizi SJ. *Therapies targeting DNA and RNA in Huntington's disease.* Lancet Neurol. 2017 Oct;16(10):837-847.
15. McCusker EA, Loy CT. *Huntington Disease: The Complexities of Making and Disclosing a Clinical Diagnosis After Premanifest Genetic Testing.* Tremor Other Hyperkinet Mov (N Y). 2017 Sep 6;7:467.
16. Epping EA, Kim JI, Craufurd D, Brashers-Krug TM et al and PREDICT-HD Investigators and Coordinators of the Huntington Study Group. *Longitudinal Psychiatric Symptoms in Prodromal Huntington's Disease: A Decade of Data.* Am J Psychiatry. 2016 Feb 1;173(2):184-92. Epub 2015 Oct 16.

Updated criteria for diagnosing Multiple Sclerosis

Peter Brex
MB BS, MD, FRCP is a Consultant Neurologist at King's College Hospital NHS Foundation Trust. He trained in London and was appointed to his current role in 2005. He specialises in multiple sclerosis, with a particular interest in early prognostic markers and the management of MS during pregnancy.

Victoria Williams
has been a Consultant Neurologist since 2009. She is an MS specialist at Guy's and St Thomas' and King's College Hospitals NHS Trusts.

Correspondence to:
PA Brex,
Department of Neurology,
King's College Hospital NHS Trust,
Denmark Hill,
London
SE5 9RS.

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Key take home messages

- The diagnostic criteria for MS have been recently updated
- These criteria should only be applied to populations in whom MS is common and patients who present with typical symptoms for which no better explanation can be found
- All patients with suspected MS should have an MRI brain scan; spinal cord imaging is not mandatory
- Unmatched oligoclonal bands in the CSF can be used as a substitute for demonstrating dissemination in time, allowing an earlier diagnosis than was previously possible

Abstract
The fourth update of the McDonald criteria enables an earlier diagnosis of MS in people presenting with typical symptoms. It broadens MRI evidence for dissemination in space to include symptomatic and cortical lesions and allows dissemination in time to be demonstrated by unmatched oligoclonal bands in the CSF as well as by new or enhancing MRI lesions. To avoid misdiagnosis, it should be used with caution in patients with atypical symptoms or in populations in which MS is uncommon.

The history of diagnostic criteria for multiple sclerosis (MS)

Multiple Sclerosis (MS) became widely recognised after Jean-Martin Charcot (1825 – 1893) (Figure 1a) described it in his lectures in the late 18th century. Prior to this patients with MS would typically have been described as having a palsy, paralysis or paraplegia, without much understanding as to the cause.

In May 1960, a symposium on the 'Evaluation of Drug Therapy in Neurologic and Sensory Diseases' held at the University of Wisconsin concluded that criteria for MS were required to provide a common ground of terminology amongst investigators to facilitate therapeutic trials.

A committee of experts chaired by George Schumacher (1912 – 2008) was formed and published the Schumacher criteria in 1965.[1] This enabled a diagnosis of definite MS in

- a typically aged individual (defined as between 10 and 50 years)
- with a compatible history – attacks lasting at least 24 hours, separated by at least a month; or in the case of progressive MS, a slow or stepwise progression of disability over a period of at least six months
- and objective clinical evidence of lesions in two or more distinct sites in the white matter of the central nervous system
- with no more satisfactory explanation.

The Schumacher criteria were purely clinical, although investigations were encouraged (blood, urine, chest X-ray, CSF analysis) to exclude alternative conditions.

Over the next few years modifications to the Schumacher criteria were published[2,3] but in 1983 the Schumacher criteria were replaced by criteria developed by a committee chaired by Charles Poser (1923 – 2010).[4] The Poser criteria incorporated laboratory and clinical tests developed in the previous decade to support the diagnosis with 'paraclinical evidence' of lesions. This included evoked potentials, computed tomography (CT) or NMR scans (as MRI was known in its early days), as well as induced hyperthermia (the hot bath test) and expert urological assessment. The acceptable age of onset was extended to 10 to 59 years of age. The criteria emphasised that symptoms should be consistent with MS and the diagnosis made by a 'competent neurologist'.

The criteria divided patients into two groups – 'Definite' and 'Probable' MS – each with two sub-groups – 'Clinical' and 'Laboratory-supported'; the latter referring to the presence of oligoclonal bands or raised IgG in the CSF. Clinically Definite MS became the requirement for entry into therapeutic trials of the time and required two attacks and objective clinical evidence of two lesions; or two attacks with objective evidence of one lesion and paraclinical evidence of another separate lesion. Certain historical symptoms could be substituted for clinical evidence in some instances, e.g. Lhermitte's phenomenon in the absence of cervical spondylosis; painful optic neuritis in an under 50-year-old, trigeminal neuralgia in an under 40-year-old.

In 2001, Poser's criteria were replaced by McDonald's criteria,[5] developed by the International Panel on MS Diagnostics, chaired at their first meeting by Ian McDonald (1933 – 2006) (Figure 1b). These criteria placed a much greater emphasis on the use of MRI lesions (areas of T2 hyperintensity at least 3mm in cross-section) to demonstrate dissemination of disease in space and time. These criteria enabled a diagnosis of MS after a single clinical attack which allowed clinical trials to include patients at a much earlier stage than had previously been possible. Progressive MS, which had not been

Figure 1a: Jean-Martin Charcot (1825 – 1893).

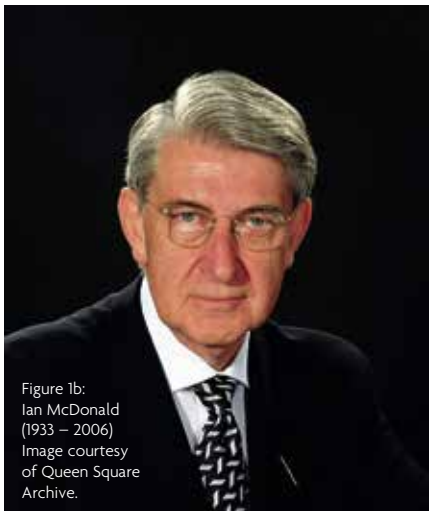

Figure 1b: Ian McDonald (1933 – 2006) Image courtesy of Queen Square Archive.

Table 1. New diagnostic criteria for RR MS[8]

Number of clinical attacks*	Number of lesions with objective clinical evidence	Additional evidence required
≥ 2	≥ 2	None
≥ 2	1 plus good historical evidence	None
≥ 2	1	Dissemination in space by a further clinical episode at another site or by MRI
1	≥ 2	Dissemination in time by a further clinical episode, by MRI or the presence of CSF oligoclonal bands
1	1	Dissemination in space by a further clinical episode at another site or by MRI AND Dissemination in time by a further clinical episode, by MRI or the presence of CSF oligoclonal bands

*attacks should be separated by at least 30 days between onset

Table 2. New diagnostic criteria for PP MS[8]

1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse.

Plus two of the following criteria:

- One or more T2-hyperintense lesions characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions in the spinal cord
- Presence of CSF-specific oligoclonal bands

addressed by the Poser criteria, was defined in McDonald's criteria and required the presence of oligoclonal bands or raised IgG index in the CSF supported by typical MRI findings +/- delayed visual evoked potentials (VEPs) and dissemination in time demonstrated either by progression of disability over a year or new MRI lesions.

The McDonald panel have subsequently met approximately every 5-years to refine and simplify the criteria.[6,7] The number of lesions required to provide evidence of dissemination in space have been reduced and evidence of dissemination of disease in time may be obtained from a single MRI with both enhancing and non-enhancing lesions. The criteria for progressive MS were changed so that insidious neurological progression became the main requirement and oligoclonal bands or elevated IgG index in the CSF were no longer mandatory if there were typical MRI findings in the brain and spinal cord. The term 'possible MS' was added for people with a typical clinically isolated syndrome who did not meet the criteria.

The 2017 revisions to the McDonald criteria

Following meetings in November 2016 and May 2017 the fourth version of the McDonald criteria was published in *Lancet Neurology* in January 2018.[8] This panel was expanded to include additional expertise in clinical, imaging and laboratory aspects of MS diagnosis, and to address criticisms that they were only applicable to European and North American populations, included a broader representation from different geographical regions. Changes to the diagnostic criteria were evidence-based and not just based on expert opinion.

The most significant change is the revitalisation of the role of CSF analysis. The finding or tfo or more oligoclonal bands was found to be more reliable than a raised IgG index and their presence has been shown to have high predictive value for conversion from clinically isolated syndromes to MS. The panel agreed the presence of unmatched oligoclonal bands in the CSF could confirm dissemination in time in place of clinical or MRI evidence. The panel also stressed the importance of CSF in excluding MS mimics.

The MRI criteria for dissemination in space have also been changed. Cortical lesions can now be counted in place of juxtacortical ones when assessing for lesions in one of the four typical sites (the others sites are periventricular, brainstem or spinal cord lesion). However, cortical lesions are not well appreciated on currently available clinical MRI scans conducted outside of research and so this will not have a great impact on most clinicians. The panel did not increase the number of periventricular lesions required, as was recommended in a 2016 MAGNIMS MRI criteria paper,[9] but suggested this may be advisable in older patients and those at high risk of having white matter lesions, e.g. vascular risk factors, migraine. They did allow for the inclusion of symptomatic lesions when assessing for radiological evidence of dissemination in space – an exception being high signal in the optic nerves in people with optic neuritis.

As with the criteria that have predated it, the McDonald criteria do enable MS to be diagnosed without the need for any supporting investigations, but the panel recommended all patients in whom a diagnosis of MS was being considered should have an MRI brain. An MRI of the cord is not mandatory but advisable when signs localise to the cord, in progressive MS and in populations in whom MS is more unusual.

Whilst the sensitivity and specificity of the McDonald MRI criteria have been shown to be high when applied to patients with typically clinically isolated syndromes suggestive of MS,[10] there have been a number of papers published demonstrating that they over-diagnose MS in a 'real world' setting.[11-13] The McDonald criteria were not developed to diagnose MS in patients with atypical symptoms or to distinguish it from other conditions which can cause high signal in the white matter lesions on MRI, e.g. acute disseminated encephalitis (ADEM), neuromyelitis optica spectrum disorders (NMOSD), vascular disease, migraine and even normal ageing. Caution should be exercised in people outside the typical presenting age for MS (although MS can present in childhood and in individuals over 60 years) and in ethnic groups in whom MS is uncommon. The benefits of expert neuro-radiological input cannot be over-emphasised.

A diagnosis of multiple sclerosis should never be made based on MRI appearances

alone, although some patients with these so-called Radiologically Isolated Syndromes will develop typical symptoms of MS in time[14] and may require counselling and follow-up.

Application of the 2017 revised McDonald criteria in patients with typical clinically isolated syndromes followed up for five years has been demonstrated to have greater sensitivity but less specificity for a second attack than the 2010 criteria with similar accuracy.[15] This means it will diagnose more patients with less active MS.

In conclusion, the McDonald Criteria are helpful in providing an accurate and earlier diagnosis of MS in patients following a single attack with typical symptoms, however when the presentation is atypical, or in populations in which MS is uncommon, investigation should be extended beyond MRI, with a low threshold for further investigation, particularly examination of the CSF.

REFERENCES

1. Schumacher GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, Mcdowell F, et al. *Problems Of Experimental Trials Of Therapy In Multiple Sclerosis: Report By The Panel On The Evaluation Of Experimental Trials Of Therapy In Multiple Sclerosis.* Ann N Y Acad Sci. 1965 Mar 31;122:552–68.
2. Rose AS, Ellison GW, Myers LW, TOURTELLOTTE WW. *Criteria for the clinical diagnosis of multiple sclerosis.* Neurology. 1976 Jun;26(6 PT 2):20–2.
3. McDonald WI, HALLIDAY AM. *Diagnosis and classification of multiple sclerosis.* Br Med Bull. 1977 Jan;33(1):4–9.
4. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. *New diagnostic criteria for multiple sclerosis: guidelines for research protocols.* Ann Neurol. Wiley Subscription Services, Inc., A Wiley Company; 1983 Mar;13(3):227–31.
5. McDonald WI, Compston A, Edan G, Goodkin D, Hartung H-P, Lublin FD, et al. *Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis.* Vol. 50, Annals of neurology. 2001. pp. 121–7.
6. Polman CH, Reingold S, Edan G, Filippi M, Hartung H-P, Kappos L, et al. *Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria".* Ann Neurol. Wiley Subscription Services, Inc., A Wiley Company; 2005 Dec;58(6):840–6.
7. Polman CH, Reingold S, Banwell B, Clanet M, Cohen J, Filippi M, et al. *Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.* Ann Neurol. 2011 Feb;69(2):292–302.
8. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. *Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria.* Lancet Neurol. 2017 Dec 21;17(2):162–73.
9. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, et al. *MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines.* Lancet Neurol. Elsevier; 2016 Jan 25;0(0):292–303.
10. Brownlee WJ, Swanton JK, Altmann DR, Ciccarelli O, Miller DH. *Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria.* J Neurol Neurosurg Psychiatr. BMJ Publishing Group Ltd; 2015 May;86(5):584–5.
11. Whiting P, Harbord R, Main C, Deeks JJ, Filippini G, Egger M, et al. *Accuracy of magnetic resonance imaging for the diagnosis of multiple sclerosis: systematic review.* BMJ. British Medical Journal Publishing Group; 2006 Apr 15;332(7546):875–84.
12. Solomon AJ, Bourdette DN, Cross AH, Applebee A, Skidd PM, Howard DB, et al. *The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study.* Neurology. American Academy of Neurology; 2016 Sep 27;87(13):1393–9.
13. Rosenkranz SC, Kaulen B, Neuhaus A, Siemonsen S, Köpke S, Daumer M, et al. *Low clinical conversion rate in clinically isolated syndrome patients - diagnostic benefit of McDonald 2010 criteria?* Eur J Neurol. 2018 Feb;25(2):247–9.
14. Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, et al. *Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome.* Neurology. 2009 Mar 3;72(9):800–5.
15. Van der Vuurst de Vries RM, Mescheriakova JY, Wong YYM et al. *Application of the 2017 Revised McDonald Criteria for Multiple Sclerosis to Patients With a Typical Clinically Isolated Syndrome.* JAMA Neurology 2018; doi:10.1001/jamaneurol.2018.2160

A Lab of One's Own: Science and Suffrage in the First World War

Author: Patricia Fara
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Reviewed by: Sophia Joyce, Division of Medicine, UCL and David J Werring, Stroke Research Centre, Department of Brain Repair and Rehabilitation, Queen Square Institute of Neurology, London UK.

A Lab of One's Own is a fascinating and compelling look not just at the stories of several unsung female pioneers in science, medicine and engineering during World War One, but at the struggles of the Suffragette movement amidst a backdrop of entrenched and pervading gender stereotypes, such as those held by the renowned scientist Charles Darwin.

Fara states that from the turn of the twentieth century "To demonstrate their modernity, suffrage supporters allied themselves with scientific and technological progress." Indeed, Sylvia Pankhurst aligned technology with universal emancipation and although seemingly simple inventions, such as the bicycle, gave some women a little freedom of independent travel, and though the typewriter provided an acceptable way for a single woman to earn a living away from the drudgery of domestic servitude, it was not until World War One that women's traditional roles in society were first challenged.

Drawing on Virginia Woolf's 1929 essay, "A Room of One's Own", in which Woolf discusses how women might redefine themselves outside their traditionally subservient and economically dependent roles, the author explores the immense hurdles women had to overcome to enter the hitherto impenetrable realm of men, not just to gain the right to a university degree, but by rallying against widely held attitudes that 'education can do little to modify her nature' and that studying was bad for a woman's health.

It is common knowledge that women worked in nursing, munitions, or kept the home fire burning while their husbands fought in the trenches, but Fara expands this view by describing their work in laboratories, aeroplane production and chemical research, with Suffragettes temporarily holding a truce to invest their energies into supporting the war effort. During the War, female scientists were able to thrive in many previously inaccessible posts. Women such as Ruth King, who studied picric acid (explosives), Marie Stopes (increasing coal production and making mines safer), Frances Micklethwait (chemical weapons) and Beatrice Mabel Cave-Brown (aeroplane design) are but a few mentioned who had fascinating war careers. New medical fields of radiography and physiotherapy also flourished during the war, thanks to pioneering efforts by women to treat soldiers in the field and at home. The War also allowed women to study on scientific, technology, engineering and medicine university courses in much greater numbers than had previously been possible.

On the whole, men and women resumed their traditional gender roles after Armistice Day. However, as Fara rightly asserts, what changed forever was the traditional understanding of gender roles. With the Representation of the People Act of 1918 finally giving women over the age of 30 (who owned property) the right to vote, they were rewarded, in part, for their huge contribution to the war effort. It is worth noting that it also finally entitled all men over the age of 21 to vote, thus helping to contract the class divide somewhat. And, in large part due to the tireless efforts of Ida Smedley and Martha Whitely, women began to be admitted to professional societies (the Chemical Society) soon after the War, in 1920.

This thought-provoking book should be of interest to the scientist and non-scientist alike as women continue to fight for equality in the workplace and across society today. With regard to the medical profession, Fara states that "women were paid less than men for doing the same work, passed over for promotion and excluded from medical societies". Even today, despite a predominantly female workforce, including at senior levels, nine out of ten NHS Trusts have a gender pay gap.[1] Moreover, a recent survey of 1700 neurologists in the United States found that men outnumber women at all faculty ranks in top-ranked academic Neurology programmes, and that this discrepancy increases with advancing rank.[2] As the author writes "What happened a century ago is important for understanding the present."

A very slight irritation is that, although the author includes a brief mention of Anna Airy, one of the first women to be commissioned as a war artist, a lithograph by the renowned Christopher R.W. Nevinson has been used as the front cover. Female artists, as well as female scientists, continue to suffer lack of recognition!

References

1. https://www.theguardian.com/society/2018/mar/27/nhs-councils-gender-pay-gap-deadline (accessed 14 October 2018).
2. McDermott M et al. JAMA Neurol. 2018;75(8):956-61.

Neurovisions

Nikolas Rose,
Department of Global Health and Social Medicine, King's College London, UK.

Caitjan Gainty,
Department of History, King's College London, UK.

This issue's ACNR cover shows stills from films on the Neurovision website. See www.neurovision.org.uk

Photo credits:

1. Films of Kurt Goldstein, Kurt Goldstein Papers, 1900-1965, Series, IV, Box 18, Rare Book & Manuscript Library, Columbia University Libraries.
2. Reynolds EH, Healy DG and Lees AJ. 'A film of patients with movement disorders made in Queen Square, London in the Mid-1920s by Samuel Alexander Kinnier Wilson'. Movement Disorders 2011;26(14):2453-2459.

How do neurologists learn to look and to see? How does the 'gaze of the neurologist' determine difference or pathology? Trained experts, whether they be medical doctors or ornithologists, see the world differently from those who lack their training. Indeed, training is, in good part, learning to see.[1] So what is it that the Neurologist sees, as a result of their professional clinical training in habits of looking, that those in other areas of medicine and science, and outside these realms altogether, don't?

In 2016, we (a sociologist and a historian) decided to explore this question. In part, our 'neurovisions' project built on work one of us (Rose) had already done to explore and elucidate the birth of the 'neuromolecular' gaze: a way of looking that envisages the internal mental world of the patient in terms of the activity of neurons, neurotransmitters, and neural circuits and their normal and abnormal structure and function.[2] This 'gaze' has become increasingly familiar to non-specialists, via the public circulation of images like brain scans which, we are told, enable us to see the mysteries of the brain from dementia to musical appreciation. Yet, in important ways, these images, like all images, are not the thing itself. Rather brain scans and other medical images are always only visual representations, able to offer one – but never the only - way of reflecting, re-imagining, re-creating disease.

Indeed, one does not even need to look very far back to find an approach in tension with our contemporary inclination to render neurologic difference and pathology as the result of events occurring at the molecular level. Towards the end of his life, the great Neurologist Alexander Romanovich Luria described the approach that he had taken in The Man With A Shattered World and The Mind of the Mnemonist[3] as 'romantic science'.[4] Oliver Sacks explicitly followed this genre: in his introduction to the 1987 edition of *The Man With A Shattered World*, he described his approach of melding the synthetic biography of the individual case with clinical analysis as "the dream of a novelist and a scientist combined".[5] As the historian Anne Harrington has pointed out, this was also the way that the world of the neurodiverse – to use the current term – was portrayed in such movies as *Rain Man* (a savant with mental disabilities) and *The Curious Incident of the Dog in the Night-time* (the world of a young man diagnosed with Aspergers).[6] Examining this evidence, Harrington suggested that some Neurologists had been less concerned with the question of "what mechanisms have gone wrong" and more with "what is it like to be a person with a brain injury, Alzheimer's disease, autism, or Tourette syndrome."[6] This seemed good in theory, we thought, but what did holism look like in practice? What were the practices of neurologic looking that this 'romantic' approach required? Were these practices a more 'holistic' mode of apperception of the patient and the world that he or she inhabited?

These questions led us to the five short films of the Psychiatrist/Neurologist Kurt Goldstein (1878-1965), whose career spanned the middle decades of the twentieth century. We were drawn to Goldstein's films not only because they fit the general chronology of the 'romantic science' of neurology, but also because Goldstein himself was explicitly committed to holism. Pushing back against the tendency toward localism in his own time, Goldstein argued that neurological injury refashioned the brain as a whole, so that the orientation of the patient's body, self and relation to the world also of necessity changed.[7] "The better we became at observing,' Goldstein noted, 'the more we came to ascertain that more or less none of the actions are performed normally anymore after a lesion in the nervous system".[8] Goldstein's mode of neurological looking thus emphasised the crucial importance of multiple, not singular, diagnostic tests. Though Goldstein saw his therapeutic role as facilitator of the brain's subsequent 'healing,' this was not primarily aimed at the restoration of function. Instead, Goldstein's 'therapy' largely consisted of the creation of a new attitude of the body towards its environment.

Goldstein was greatly aided in his work by the use of the motion picture camera, which was widely regarded among scientific and medical communities of this era as an instrument both fundamentally-attuned to scientific work and clinically multifaceted. The still camera had been a mainstay of Neurologists in the nineteenth century, so that when the famed physiologist and cinematographer Étienne-Jules Marey (1830-1944) helped to install the motion picture camera at the Salpêtrière, this was in some ways the extrapolation of a much longer visualising tradition. But the motion picture camera transformed the work done by its still forebear in one radical way: its ability to capture and retain motion, that most ephemeral yet fundamentally critical bellwether of neurologic pathology.

Like his contemporaries, Goldstein understood the motion picture's significance not only as documentation, but as active diagnostic, therapeutic and pedagogic intervention.[9] Diagnostically and therapeutically, filmmaking made possible the capturing of Goldstein's 'holism' in the first place, since it could show patients interacting with their environments that the still photo or case report could not. We meet patients not only as the subjects of Goldstein's testing, but crucially also en passant, catching glimpses of the constant accommodation of their neurologic to their lived selves as they happen. Goldstein used the unique capabilities of the camera not only to capture but also to edit and construct motion. And in this way, his vision of neurologic pathology as an ephemeral, unstable and dynamic phenomenon was given fullest articulation by film. Film also created a richer pedagogical experience. For, watching these films was not intended as a passive process of witnessing or commenting on a procedure or course of neurologic action.[10] Instead, like many medical films of this period, Goldstein's films also offered an active and immersive education in a specific - neurological - way to see. To watch these films was to learn to see as Goldstein did: to acquire the necessary habits of looking that made these films make sense.

What we found fascinating when examining Goldstein's films, however, was not just the the empirical grounding in neurologic practice – the 'deromanticising' - of neurology's romance they accomplished. It was also, perhaps more, their illegibility to current practicing Neurologists.[11] Some measure of distance would, of course, be presumed between past prac-

tices of looking and ours today. No amount of looking at Goldstein's films, despite their intended pedagogic workings, could shift the foreignness of his vision. These did not seem compatible, even as historical precursors, to contemporary neurological looking practices.

The current unintelligibility of these films confirms what we already theorise, that habits of looking are never 'natural' or 'objective' but instead culturally constructed, deeply contextual acts. The style of looking evident in these films seems so unnatural and counter-intuitive to us now that we instantly understand them as a constructed artefact. Embedded in this recognition is the tacit acknowledgment that our own practices of neurological looking must also be constructed and historically specific. In the process of learning to 'see' properly, contemporary Neurologists, like Goldstein, see their own processes as 'natural,' objective, as the development of a vision of what is really there. But in fact, learning to see requires the cultivation of a productive myopia, in which certain things are obscured and others highlighted as suits our current notions of neurological disease, our current predispositions toward certain explanatory structures. In this sense, Goldstein's cinematographic exercises are consistent with ours today, emphasising as they do not what is seen but the significance of the focusing of sight as a timeless, fundamental neurologic act.

These 'neurovisions' – these ways of getting the full picture of a neurological disorder – have shifted alongside medicine and neurological practices. It is these larger processes of seeing that we seek to unearth in our current research. Though we initially understood "neurovision" as quite specifically bound up in the act of seeing neurologically itself, more recently, we have understood that seeing neurologically is not merely a visual practice. Even with Goldstein, the patient was put through specific tests or procedures to 'render visible' the consequences of the injury, to intensify them so that they were clearer to the observer, even to force into visibility some symptoms that would not, in the ordinary course of events, be visible. Today, what might once have been thought of as the simple act of skilled observation, as portrayed in Rembrandt's famous 1632, The Anatomy Lesson of Dr. Nicolaes Tulp, is insufficient. It is true, as Andrew Lees has pointed out,[12] that the Neurologist is a kind of detective, in search of the clues that will identify the 'villain' – the lesion or internal anomaly responsible for the ailment of the patient. But he or she no longer stands alone in front of the patient, trained vision informed only by the 'case history'. The expert gaze must be amplified and supplemented by images provided by, and often interpreted by, a range of other technologists. We invest our hopes and beliefs in X-ray, CT, MRI, fMRI and all of the other technologies capable of augmenting our vision. But they are not only augmentations. These technologies actually do more: they change the scale at which the Neurologist sees the condition and the form in which its origin is conceptualised. Today, there is also a new relation of time to vision: the push to diagnose diseases earlier, the belief that 'earlier is almost always better' when it comes to making a person into a patient – identifying a prodrome which can reveal that he or she is 'presymptomatically ill' – means that different kinds of looking, for different kinds of signs and symptoms, is required. This shifted temporality has, in turn, shifted what counts as a symptom. Small differences of function, that might otherwise be considered well within the realm of normal variation, now carry with them the potency of future pathology.

Perhaps the most radical shift has occurred in clinical genetics. No longer content merely to establish a disorder's genetic cause by charting its occurrences across a lineage, the neurological gaze has shifted once more. It no longer focuses on the external symptoms of disease perceived by the patients themselves or others around them – however slight, however nascent. New technologies of gene sequencing have rendered the invisible visible, and refocused clinical attention on those small variations in gene sequences that, in some but not all cases, will eventually reveal themselves in symptoms. Despite the rhetoric of precision and 'personalisation' associated with the predictive power of contemporary molecular genetics, the person so diagnosed now enters a world of probabilities and uncertainties. They are, as it were, 'patients in waiting'. Will they get sick, when will they get sick, how quickly will their disease progress, when is early intervention warranted, how will these 'genetic instructions' play out in their own, singular, individual body and brain? If, as we know, these questions haunt those with a family history of single gene disorders such as Huntington's Disease – so much that around half of those with such a family history of neurological disorder refuse to take the genetic test – how much more so for the disorders whose genetics is multiple, probabilistic, developmental and contingent on many other factors for its emergence. What is the neurological gaze, then, in these proliferating conditions of uncertainty?

Then there are the disorders which we cannot 'see' at all; where none of our technologies reveal anomalies. Can we still think of some disorders as 'functional'? What is the status of a disorder that only exists in the sometimes erratic narratives of a patient's story? When it comes to Chronic Fatigue Syndrome, Gulf War Syndrome and many more conditions characterised by a somewhat confused concatenation of neurological, mental and physical complaints, are we confronted with 'real' disorders even though our current practices of looking don't see it? Or is it something that the patient has acquired 'culturally', simply an embodiment of a "cultural construction"? Are these symptoms of something else: a psychiatric disorder? Or is this a problem awaiting 'objective' confirmation? And if so, on whose authority? Must we wait for a physiological test? A more precise brain scan? Better gene sequencing? Or is it a matter of clinical 'art', the culturally-constructed gaze of the clinician, further specified by years of personal experience and a lifetime of successes and failures burned deep into the memory?

Some rather important issues are embedded within these questions about ways of seeing. Beyond the ambiguities of the distinction between functional and organic disorders, perhaps even the borders between neurology and psychiatry are at stake. If all psychiatric disorders are, in the end, to be regarded as brain disorders, and if all neurological disorders also are to be regarded, ultimately as emerging from molecular anomalies in brain and nervous system, why should the division stand? Should we not abandon the idea of a romantic, holistic science, with its respect for the experience of being a person in the world? Or, just perhaps, should the line of development be the other way round: should Neurologists resist the siren call of the new brain sciences and their claims to know, at last, the reality of the disorder, and recognise, as did Goldstein, that what was at stake for the patient was a whole new way of being in the world? In recognising that as one possible way of being a human being, we might be able to look anew at those ways of being that those of us who think of ourselves as 'normal' take so much for granted. By exploring the history of these ways of seeing, we aim not only to get a fuller picture of how and what Neurologists see, but also to explore how modes of medical looking more generally are created and continually re-defined, solving some problems and creating others with each new definition.

REFERENCES

1. See e.g. Daston L. *On Scientific Observation.* Isis, 2008;99(1):97-110.
2. Rose N, Abi-Rached J. *The birth of the neuromolecular gaze.* History of the Human Sciences, 2010;23(1):1-26.
3. Luria AR. (1972). *The Man With A Shattered World* (L. Solotaroff, Trans.) Cambridge, MA: Harvard University Press. Luria AR. (1932/1976). *The Mind Of The Mnemonist* (L. Solotaroff, Trans.). Cambridge, MA: Harvard University Press.
4. Luria AR. (1979) *The Making Of Mind: A Personal Account Of Soviet Psychology.* (Trans. and Ed. M. Cole & S. Cole.). Cambridge, MA: Harvard University Press.
5. Sacks O. (1987) *Introduction, The Man With A Shattered World,* Cambridge, MA: Harvard University Press, p. xii)
6. http://www.dana.org/Cerebrum/2005/The_Inner_Lives_of_Disordered_Brains/
7. Goldstein K. (1995[1939]) *The Organism: A Holistic Approach To Biology Derived From Pathological Data In Man*. New York: Zone Books.
8. Goldstein K. (1925) *Zur Theorie der Funktion des Nervensystems*, Archiv für Psychiatrie 74, 398.
9. Geroulanos S, Meyers T, (2014) *Experimente im Individuum: Kurt Goldstein und die Frage des Organismus*. Berlin: August.
10. See e.g., Gainty C. (2012) *Going After the High-Brows: Frank Gilbreth and the Surgical Subject.* Representations, 1-27; Ostherr K. (2013) *Medical Visions.* New York, NY: Oxford. For an older view on cinematographic roles, see Didi-Huberman G. (1993) *The Invention Of Hysteria: Charcot And The Photographic Iconography Of The Salpêtrière.* Cambridge, MA: MIT.
11. A selection of these films can be seen at our website: https://neurovision.org.uk/
12. Lees A. (2017). *Mentored by a Madman: The William Burroughs Experiment.* London: Notting Hill Editions.

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2) Data on file – Excerpts from Epistatus Patent Application.
3) Data on file (item code EDM/1030/2017), Veriton Pharma Ltd 2017.
4) Medicines Optimisation: Helping patients to make the most of medicines. Royal Pharmaceutical Society May 2013.
5) Pharmaceutical waste reduction in the NHS. NHS England, June 2015.
6) Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use.

EDM-1068-2018
Date of Preparation: November 2018

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Does insomnia worsen cardiometabolic health?

Gewei Zhu,
Bsc(Hons), MRes, is a PhD student at Newcastle University. Her project investigates the impact of insulin resistance on ageing, appearance and wellbeing using sleep as a model system.

Kirstie Anderson,
BMedSci, MBBS, MRCP, DPhil (Oxon), runs the Regional Neurology Sleep Service with a clinical and research interest in all the sleep disorders. She is an Honorary Senior Lecturer at Newcastle University with an interest in the link between sleep and mental health.

Correspondence to:
Kirstie Anderson,
Department of Neurology,
Royal Victoria Infirmary,
Newcastle Upon Tyne, UK.
E: Kirstie.anderson@nuth.nhs.uk

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Key points

- Self-reported sleep duration does not always correlate with objective sleep loss.
- The mis-match between subjective and objective sleep duration is due in part to sleep state misperception.
- Only a relatively small percentage of insomniacs with objective short sleep duration have high risk of cardiometabolic disease.

Abstract

Insomnia is thought to affect 5-10% of the general population and is associated with daytime impairment and distress. Insomniacs were found to have a higher risk of poor cardiometabolic health. However, this association is only significant if they have both insomnia and objective short sleep duration.

Introduction

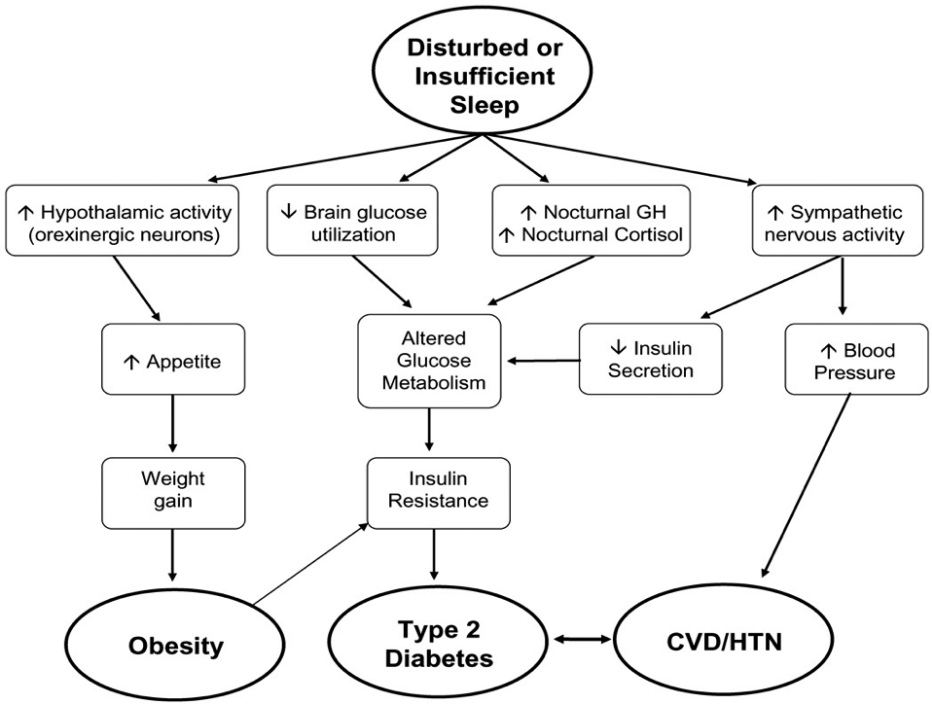
Cardiometabolic health (CMH) is an umbrella term encompassing the cardiovascular and metabolic systems. Risk factors for worse CMH include insulin resistance, hypertension, abdominal obesity and dyslipidaemia. There are substantial economic and individual burdens associated with poor CMH. It is well established that poor diet and physical inactivity have causative roles, but emerging evidence suggests that poor sleep quality and sleep deprivation also increase the risk of cardiometabolic disease (Figure 1). Sleep disturbance could be due to societal pressure such as shift work or due to specific sleep disorders such as obstructive sleep apnoea, restless leg syndrome or insomnia disorder.[1]

Insomnia remains the commonest sleep disorder affecting approximately 5-10% of the general population. Whilst commonly presenting alongside other medical and psychiatric disorders, insomnia is now recognised as a separate disorder in its own right. Insomnia disorder is defined as difficulty falling and staying asleep despite adequate circumstances for sleep with subsequent daytime distress and impairment. Most patients complain of prolonged, frustrating awakenings during the sleep period.[2]

Sleep duration can be measured subjectively using sleep diaries or objectively using the gold standard of video polysomnography (psg). Accelerometry can also be used as an objective measure, albeit less sensitive than video psg. The diagnosis of insomnia is based on poor subjective sleep quality with daytime distress rather than objectively measured sleep fragmentation. In fact, there is often a mismatch between subjective and objective sleep duration and patients may significantly underestimate total sleep time - known as "sleep state misperception".[3]

Sleep misperception is considered common within chronic insomnia. Various factors have been suggested to play a role in it, including

Figure 1. Possible association between poor objective sleep and cardiometabolic health.
(GH= Growth hormone, CVD= Cardiovascular disease, HTN= hypertension) Image taken from Knutson (2010) [1].



altered perceptual time processing, pre-sleep worry and subtle EEG changes that might not be well measured with PSG. This has led to increasing interest in Insomniacs with objective normal sleep duration compared to those with objectively short sleep. Whether the underestimation of sleep duration in insomniacs deserves a separate diagnostic category remains under debate. Sleep misperception in itself is associated with depression, anxiety and worse coping resources. In addition, people with different insomnia phenotypes may respond to different treatment approaches.[3] Here we will describe the relationship between metabolic syndromes and insomnia with both subjective and objective short sleep durations.

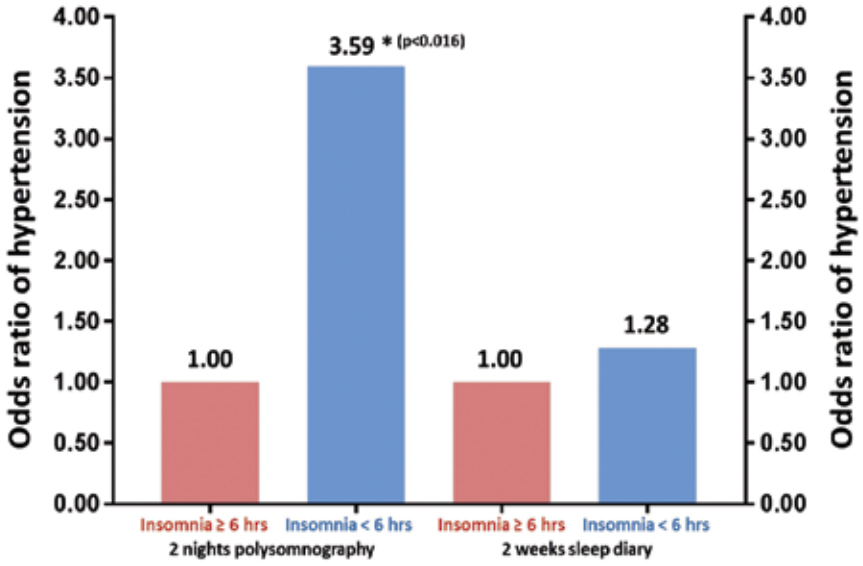


Figure 2. Adjusted odds ratio of hypertension associated with subjective and objective sleep duration. Graph produced using data from Bathgate et al. (2016) [11].

Insomnia and diabetes

Sleep disturbance is significantly associated with abnormal glucose regulation and higher incidence of type 2 diabetes (T2D).[4] However, this association could well be confounded by other factors, such as socioeconomic status, alcohol, smoking and psychiatric distress which will all increase the risk of both insomnia symptoms and T2D. A prospective cohort study investigated possible confounders and the cumulative effect of insomnia over 20 years. The results suggested that the association between sleep and diabetes were largely confounded, especially by psychiatric distress which needs further investigation.[5]

In many research studies looking at insomnia and diabetes, sleep disturbance was measured by questionnaires and obstructive sleep apnoea was not controlled for. However, an important, population-based study carried out by Vgontzas et al.[6] measured sleep objectively with PSG alongside self-report sleep diaries. They found that compared to those who slept >6 hours per night, those who had insomnia and objectively slept for ≤5 hours per night had an approximately 300% increased risk of diabetes (OR 2.95, 95% CI 1.24-7.03). While those who have no insomnia and sleep <5 hours per night only had a 10% increased risk of diabetes (OR 1.10, 95% CI 0.68-1.79). There was also a positive correlation between the severity of insomnia and the likelihood of developing diabetes. These findings suggest that objective sleep measurement in insomnia could be a useful marker for its severity and impact upon glucose regulation. The cross sectional nature of the study means a causal relationship cannot be determined.

Insomnia and cardiorespiratory fitness

A large number of studies have focused on the relationship between insomnia and mental disorders, but few have investigated the effect of insomnia on respiratory function. A large cross sectional population study examined the association between insomnia and peak oxygen uptake (VO2peak) measurement of cardiorespiratory fitness. Participants were asked to walk/run at an increasing speed on a treadmill until exhaustion and VO2peak levels were determined. As poor cardiorespiratory fitness is also closely associated with poor cardiometabolic heath, even in the absence of insomnia. Strand et al. controlled for various potentially confounding factors including BMI, blood pressure, resting heart rate, total serum cholesterol and physical activity index. They observed reduced VO2peak in people with insomnia compared to those without. The association between repeated awakenings throughout the night and VO2peak was found to be the strongest when compared to early awakening and daytime sleepiness. They also identified an inverse association between the severity of insomnia and VO2peak. As cardiorespiratory fitness is a strong risk predictor of CVD, we can anticipate a negative correlation between the severity of insomnia and cardiometabolic health.[7]

In contrast, Bonnet and Arand[8] measured overall oxygen use in insomniacs and reported an increased VO2 in people with primary insomnia compared to the controls across 24 hours. They also gave 12 adults without insomnia 400mg of caffeine three times daily for one week and participants developed insomnia symptoms including poor sleep, increased sleep latency, fatigue and anxiety. Their metabolic rates were significantly elevated as indicated by the increased VO2 level.

These two studies suggests that people with insomnia have a higher level of oxygen consumption throughout the day compared to those without insomnia. However, their peak oxygen consumption is reduced under intensive exercise, suggesting their cardiometabolic function is only reduced under physical stress.

Insomnia and cardiovascular disease

CVD is the worldwide leading cause of mortality.[9] Hypertension is a common risk factor for CVD. The negative impact of sleep disturbance on blood pressure has already been described in many epidemiological studies. Most of these only examined insomnia or short sleep based on self-report diaries.[9] However Vgontzas et al.[10] carried out a population based cross sectional study which examined the joint effects of insomnia and objective sleep duration on hypertension. The combination of chronic insomnia (insomnia complaint ≥1 year) and a sleep duration of ≤5 hours per night was found to be associated with a 500% increased risk of hypertension compared to those without insomnia and sleep for >6 hours per night. The risk of hypertension was only increased by 13% in those who had no insomnia and slept <5 hours per night. However, objective short sleep duration or insomnia alone were not found to be significantly associated with a higher risk of hypertension. Bertisch et al.[9] did a similar study which investigated the association between insomnia with objective short sleep duration and risk of CVD. They have found that participants have a 29% higher risk of incident CVD when they have insomnia with an objective sleep duration of <6 hours per night, while the association between incident CVD and subjective short sleep duration is not significant. These studies provide evidence that insomniacs with objective short sleep duration are more vulnerable to CVD but not those with only a subjective short sleep time. Therefore, both objective sleep duration and insomnia symptoms seem important for risk assessments.[9]

An American study reported higher CVD events in those with insomnia complaints every day compared to those without any complaints, and a Swedish study reported that those who had difficulty initiating sleep had a higher risk of coronary artery disease mortality.[1] Poor subjective sleep quality was associated with higher risk of hypertension. However, a cross sectional observation study by Bathgate et al.[11] reported that only objective short sleep duration was associated with a higher risk of hypertension, while the relationship was not significant with subjective sleep duration. Another study reported that lower objective sleep efficiency was strongly associated with higher prevalence of prehypertension.[1]

Based on the above studies, insomnia with objective, but not subjective, short sleep duration is associated with higher risk of CVD and hypertension.

Insomnia and obesity

Obesity is a worldwide problem, mainly caused by excess calorie intake and physical inactivity. It is associated with CVD, stroke, T2D and psychological problems.

Experimental data reported an increased level of appetite-stimulating ghrelin, decreased level of appetite-inhibiting leptin and glucose intolerance in sleep-restricted individuals.[12] Many cohort, cross-sectional and longitudinal studies have determined an association between poor sleep and obesity.[12] However, the main limitation of these studies is the lack of objective sleep measurements. Studies on sleep and obesity have been summarised in a review by Tatjana Crönlein.[12]

In contrast to the large number of studies on other sleep disorders and obesity, limited studies have investigated the association between insomnia disorder and obesity. Huang et al.[13] measured sleep using PSG in Chinese insomniac patients and healthy controls but found no significant difference in their BMI. Another study by Crönlein et al.[14] found that German patients with severe chronic insomnia even had lower BMI than controls.

Conclusion

Self-reported sleep duration is sufficient for a diagnosis for insomnia disorder, however it clearly does not always correlate with objective sleep loss due in part to sleep state misperception. There is an increased risk of hypertension and diabetes in those with insomnia but ONLY if they have an objectively short sleep time as well, this is approximately 10% of those who suffer from insomnia.[15] There is no clear link between obesity and insomnia.

REFERENCES

1 Knutson KL. *Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence.* Best practice & research Clinical endocrinology & metabolism. 2010;24:731-743.

2 Roth T. *Insomnia: Definition, Prevalence, Etiology, and Consequences.* Journal of Clinical Sleep Medicine : JCSM : official publication of the American Academy of Sleep Medicine. 2007;3:S7-S10.

3 Fernandez-Mendoza J, Calhoun SL, Bixler EO, Karataraki M, Liao D, Vela-Bueno A, Ramos-Platon MJ, Sauder KA, Basta M, Vgontzas AN. *Sleep Misperception and Chronic Insomnia in the General Population: The Role of Objective Sleep Duration and Psychological Profiles.* Psychosomatic medicine. 2011;73:88-97.

4 Knutson KL, Ryden AM, Mander BA, Van Cauter E. *Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus.* Archives of Internal Medicine. 2006;166:1768-1774.

5 Green MJ, Espie CA, Popham F, Robertson T, Benzeval M. *Insomnia symptoms as a cause of type 2 diabetes Incidence: a 20 year cohort study.* BMC Psychiatry. 2017;17:94.

6 Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. *Insomnia With Objective Short Sleep Duration Is Associated With Type 2 Diabetes: A population-based study.* Diabetes Care. 2009;32:1980-1985.

7 Strand LB, Laugsand LE, Wisløff U, Nes BM, Vatten L, Janszky I. *Insomnia Symptoms and Cardiorespiratory Fitness in Healthy Individuals: The Nord-Trøndelag Health Study (HUNT).* Sleep. 2013;36:99-108C.

8 Bonnet MH, Arand DL. *Insomnia, metabolic rate and sleep restoration.* Journal of internal medicine. 2003;254:23-31.

9 Bertisch SM, Pollock BD, Mittleman MA, Buysse DJ, Bazzano LA, Gottlieb DJ, Redline S. *Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality*: Sleep Heart Health Study. Sleep. 2018;41.

10 Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. *Insomnia with Objective Short Sleep Duration is Associated with a High Risk for Hypertension.* Sleep. 2009;32:491-497.

11 Bathgate CJ, Edinger JD, Wyatt JK, Krystal AD. *Objective but Not Subjective Short Sleep Duration Associated with Increased Risk for Hypertension in Individuals with Insomnia.* Sleep. 2016;39:1037-1045.

12 Cronlein T. *Insomnia and obesity.* Current opinion in psychiatry. 2016;29:409-412.

13 Huang L, Zhou J, Sun Y, Li Z, Lei F, Zhou G, Tang X. *Polysomnographically determined sleep and body mass index in patients with insomnia.* Psychiatry research. 2013;209:540-544.

14 Cronlein T, Langguth B, Busch V, Rupprecht R, Wetter TC. *Severe chronic insomnia is not associated with higher body mass index.* Journal of sleep research. 2015;24:514-517.

15 Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. *Insomnia with Objective Short Sleep Duration: the Most Biologically Severe Phenotype of the Disorder.* Sleep medicine reviews. 2013;17:241-254.

Taking the scenic route through training…

Helen Grote

is a Neurology Registrar at Imperial College Healthcare NHS Trust, UK. She undertook preclinical medicine at the University of Oxford, followed by an intercalated D.Phil and clinical training at the University of Cambridge. Prior to starting Neurology Training, she worked as a Clinical Genetics Registrar at St. George's Hospital NHS Trust, and retains a sub-specialist interest in neurogenetics. Alongside her Neurology training, she also works as a Fitness to Practice Tribunal Member with the Medical Practitioners Tribunal Service (MPTS) and is currently undertaking an OOPE as Clinical Fellow to the Chief Inspector of Hospitals at the Care Quality Commission through the National Medical Director's Clinical Fellow Scheme.

In the words of a colleague, I am taking the 'scenic route' through Neurology training – mainly to develop my own professional interests, but also out of a recognition that, increasingly, being a Consultant requires more than just an ability to assess, diagnose and treat neurological conditions. Whilst the leadership and management aspect of the curriculum can be achieved through a weekend course and lectures on the topic, in real life, there is no substitute for experience in this area to prepare trainees for the 'add-on' roles increasingly demanded of Consultants; chairing meetings, writing business plans, supervising trainees, dealing with complaints, preparing for CQC inspections… and so the list goes on. Furthermore, the structure of Neurology training means that trainees typically spend their entire training in a hospital environment, sometimes with little understanding of how guidelines are developed, policy is implemented and funding decisions made in the wider NHS.

So...How can trainees pursue extra-curricular activities aligned with their career ?

I was initially a member of the BMA Junior Doctors Committee from 2008-2012, and sat on the executive committee for Education and Training. During this time I had the opportunity to chair meetings, as well as attend external meetings at the GMC and the Department of Health. This provided my first insight into the role of Arms Length Bodies (ALBs) in setting standards in healthcare, shaping health policy and training the future workforce.

The BMA and other ALBs provide opportunities for trainees to be engaged in policy development, organising conferences and writing articles (see page 23). Whilst most of these appointments are usually for voluntary roles, basic expenses are typically covered and food provided.

The networking opportunities available through such organisations are as valuable as the skills obtained; meeting with like-minded colleagues invariably provides opportunities for collaboration and a forum in which further opportunities are advertised. It was through colleagues at the BMA that I first learned about the MPTS, and the National Medical Director's Clinical Fellow Scheme.

Working for the Medical Practitioners Tribunal Service

In November 2014, I saw an advert in the BMJ for Fitness to Practice Tribunal Members at the MPTS. The advert – particularly welcoming applications from 'women, anyone under 40, anyone with a disability, and ethnic minorities' encouraged me to apply for a role that I had

assumed was reserved for senior Consultants. Following submission of a lengthy application form, I was invited to a selection centre in Manchester, where there was an interview, a written paper with questions on a scenario involving allegations against a doctor, and a critical reasoning test.

The MPTS holds recruitment rounds every 2-3 years. There were 350 applicants in the last round, and 50 were appointed. The appointment term is for four years, extendable for another four years. Appointed tribunal members are expected to commit to a minimum of 20 days per year.

I had support from my educational supervisor and training programme director, who both recognised that this experience does help develop competences allied to the curriculum. I am paid a fixed daily rate by MPTS and take unpaid leave from my NHS post for the weeks while I am away.

I typically spend a fortnight in Manchester every six months, but there are options for tribunal members to be listed for shorter review hearings lasting 1-3 days. Each tribunal has three members on the panel; a medical member, a lay member, and a chair who can be from a medical or lay background. In the absence of a legally qualified chair there is also a legal assessor present. We listen to the evidence presented by the barrister for the GMC, the doctor and their representative (if present), as well as consider written evidence from a variety of sources including police statements, performance reviews, testimonials from colleagues, and sometimes oral evidence from expert witnesses and patients.

The role of a fitness to practice panellist has been a challenging one; cases I have dealt with cover a range of misconduct including sexual and physical assaults, human trafficking, and theft of medications and property. I do not take it lightly that we suspend, and even erase doctors from the register, as I know full well the hurdles of medical school, training applications, postgraduate exams and unsociable working hours required to progress in a medical career. However, the public needs to have confidence in the reputation of the profession, and protection from the small minority of doctors who harm patients. To put this into context, there are approximately 270,000 doctors on the register, ~ 237 are referred to a fitness to practice tribunal each year, of which 70-75 each year will be erased.[1]

Following each hearing, the tribunal produces a determination – a lengthy document that sets out the reasoning for our decisions at each stage of the hearing; facts, impairment and sanction. These are made publically available on the MPTS website www.mpts-uk.org.

Fellowship schemes

Whilst it has been commonplace for Neurology trainees to take time out for research, there are also an increasing number of leadership and management schemes, including the RCP's Chief Registrar Scheme, Darzi fellowships, and The National Medical Director's Clinical Fellow Scheme.

I had been aware of the latter scheme for a number of years; it provides doctors (post FY2 and above), the opportunity to spend a year working for an ALB, alongside a programme of leadership and management training provided by the Faculty for Medical Leadership and Management (FMLM). The programme appealed to me as an opportunity to do something different for a year (having progressed straight from FY1 to ST7 without a break in training), to develop my leadership skills and gain a broader understanding of how the complex network of NHS hospitals, CCGs, GP practices, STPs and ALBs all work together.

There are 35 fellows on the scheme this year – placed with a number of organisations including NHS Improvement, NHS England, the GMC, NICE, CQC and the Health Foundation. The post with the hospitals directorate at CQC was my first choice placement; I could see the relevance of the CQC work to my day-to-day job, and I felt that this environment, with its emphasis on patient safety and quality improvement would be an ideal one in which to develop 'soft' skills that would be relevant to my future clinical practice.

At present, I divide my time between going on hospital inspections, and attending meetings at the CQC, and other civil service departments. I am involved in a variety of workstreams covering everything from improving the inspection process, and the intelligence framework (such as outliers on national audits) which inform CQC inspections and helping to improve the engagement of CQC with junior doctors. The work is intellectually stimulating, although I've been surprised at how much I've missed my patients and colleagues in the NHS. However, the ongoing existence of rota gaps has provided the opportunity to do ad hoc locums, and the flexible working environment offered by CQC has enabled me to continue with ongoing audit and QI projects.

Despite some accusations of turning to the 'dark side', my colleagues here at CQC – and in allied government departments – are intelligent, driven, and equally passionate about improving care for patients, even if they're not delivering it on the frontline of the NHS. Furthermore, the network of clinical fellows, across a variety of government departments has been a useful 'hive mind' through which to glean useful nuggets of information and make valuable contacts.

Travelling to different hospitals on inspections has also provided a valuable insight into what works well (and what doesn't), and has reinforced just how much of quality in healthcare flows from good leadership.[2] I'm gradually collecting a trove of ideas I'm hoping to implement, and I hope that my skills in leadership will enable me to help shape future workplaces into ones where staff – of all grades and disciplines – work collaboratively, feel valued, and are empowered to improve the quality and safety of care we provide for patients.

The following organisations provide opportunities for trainees to sit on committees, organise conferences and develop policy. Details about appointments can usually be found through their websites.

- **British Medical Association:** engagement through the regional junior doctors committee, or attendance at the annual representative's meeting (ARM) provides opportunities to be appointed to other committees.
- **Royal Colleges:** The RCP and RCPE both have trainees committees, and may also advertise opportunities to be a question-writer for postgraduate examinations.
- **Association of British Neurologists:** has a trainee committee, with representatives from different regions. They represent the views of Neurology trainees to the ABN, and other organisations. Most other specialty organisations have similar committees.
- **Deanery training reps:** Each training Programme Director will typically seek regional reps for feedback on issues affecting trainees. Vacancies are typically advertised by the deanery.

Some organisations advertise paid roles, which junior doctors may be appointed to:

- **Care Quality Commission:** The CQC has a cohort of junior doctor specialist advisors who may be asked to assist on inspections on an ad-hoc basis. Vacancies are advertised at https://www.cqc.org.uk/jobs-cqc
- **Medical Practitioners Tribunal Service:** fitness to practice panellists: Open competition rounds are typically held every two years. See www.mpts-uk.org for details of vacancies.
- **General Medical Council:** quality assurance groups are tasked with inspecting medical schools. These teams typically have a junior doctor on board. Vacancies are also advertised for PLAB examiners and performance assessors. See https://jobs.gmc-uk.org

References

1. Medical Practitioners Tribunal Service. MPTS Report to Parliament 2017. Available from: https://www.mpts-uk.org/MPTS_Report_to_Parliament_2017.pdf_76027856.pdf [Accessed 9th November 2018]
2. Care Quality Commission. *Quality Improvement in Hospital Trusts: Sharing learning from trusts on a journey of QI.* Available from: https://www.cqc.org.uk/sites/default/files/20180911_QI_hospitals_FINAL.pdf

Freud, forgotten Neurologist

JMS Pearce MD, FRCP
Emeritus Consultant Neurologist, Department of Neurology, Hull Royal Infirmary, UK.

Correspondence to:
J.M.S. Pearce, 304 Beverley Road Anlaby, East Yorks, HU10 7BG, UK.
Email: jms.pearce@me.com

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Abstract
For a five-year period before Sigmund Freud embarked on his original studies of psychological mechanisms, nomenclature, and psychoanalysis, he had extensive neuropathological training under von Brücke and executed research into neuronal cytoarchitecture and neural tracts. Influenced by Charcot and Theodor Meynert he carried out and published important clinical studies on aphasia and cerebral diplegia. He strived to carry his scientific discipline into his psychoanalytical work. As a Neurologist his role is underestimated.

Sigmund Freud (1856-1939) is remembered for his original studies on psychological mechanisms, nomenclature, and psychoanalysis. There is an abundant literature[1] about his work on a variety of clinical and neuropathological topics.[2] This important period (1882-1889) of the Freud oeuvre has been largely neglected.

He began his studies in Medicine at the University of Vienna in 1873, graduating MD in 1881. During this time he voluntarily took up research for the physiologist Ernst Wilhelm von Brücke (1819-92) with whom he worked for several years. In 1875, he visited his half-brothers in Manchester, and there harboured inklings of a future career in England despite his protests about English conservatism and bad weather. There followed a period of military service in 1879-80, and on graduating in 1881 he began further research in Brücke's laboratory.

For several years Freud studied and investigated neuropathology and neuroanatomy. He recognised a contractile fibrillary network of the neuron, spinal ganglia and the cytoskeleton,[3] and loops of striae surrounding the nuclei in crayfish and lamprey (*Petromyzon marinus*).[4,5,6] This confirmed the observations of Robert Remak (1815-1865) some 40 years earlier, now confirmed by electron microscopy.

In 1882 he left to earn a living in clinical medicine and was a resident at the Vienna General Hospital. There he acquired neuropathological expertise[3] from Theodor Meynert (1833-1892) and Hermann Nothnagel (1841-1905). In 1885 he was appointed to the academic post of *Privatdozent*, Lecturer in Neuropathology. In Innovative studies on the medulla, published in *Brain*, he used gold chloride to stain neural tracts and axis cylinders. In three papers he demonstrated the structure and function of the tracts between the cerebellum, inferior olivary nucleus and tract, the inferior cerebellar peduncle and the medulla oblongata.[7] This work was held in high regard.

At this time he also developed an interest in the possible benefits of cocaine, which proved disastrous, and the source of much subsequent criticism although with ophthalmologist Carl Koller (1857-1944) he had shown its value as a local anaesthetic in eye surgery.

Awarded a travelling scholarship, he studied at the Salpêtrière Hospital under Jean-Martin Charcot (1825-1893) for 19 weeks between 1885 and 1886. There, the great Neurologist hugely inspired him. Charcot's lecturing bravura and his insights into hysteria[8] and hypnosis directly determined Freud's later preoccupation with psychological mechanisms.

On return to Vienna he married Martha Bernays in 1886, and to improve the financial needs of his family, at Brücke's suggestion, he left research to begin practice as Consultant in nervous diseases, especially hysteria, at Berggasse 19, Vienna. Martha bore six children; the youngest was Anna Freud (1895-1982), a distinguished psychoanalyst in her own right.*

A Neurologist, trying to find treatment for patients with neurotic or hysterical symptoms, Freud came to believe in the repression of subconscious mental processes. He lectured in 1886 at the Vienna Medical Society endorsing Charcot's views; but his unconventional ideas were not well received.

One of his most important neurological texts (though it sold only 257 copies) was: *Zur Auffassung der Aphasien: eine kritische Studie* ('On aphasia; a critical study', 1891)[9] that reviewed the existing literature, criticising its anatomical approach. He discussed Broca's (1861) and Wernicke's (1874) respective demonstrations of expressive and receptive aphasia; he coined the term 'agnosia' for disturbances of recognition of objects, then called asymbolia. At that time, existing theories of aphasia relied on anatomical localisation which Freud disparaged, preferring a broader, neurolinguistic appraisal. He believed that a lesion in one part of the cortical region might cause change in another part of the cortex, perhaps presaging Geschwind's disconnection syndromes. The learning of language seemed to occur in the mind rather than in a restricted locus ('gap') in the brain.

In detailed letters to his friend Wilhelm Fliess (1858-1928) and to his wife he described his migraine.[10] He asserted that stimuli precipitated migraine by irritation of the meninges — an idea close to modern theories of the dural plasma extravasation and vasodilatation related to 5-HT1 receptors on its mechanisms.[11]

From the Neurology Department at the Institute for Children's Diseases, in the same year as his 'On aphasia', he published his monograph on the nature and course of cerebral palsy, including Little's disease, based on 35 personally studied cases. This led to his becoming a leading authority. Indeed, his last work in Neurology entitled *Die Infantile Cerebrallahmung* (Infantile Cerebral Paralysis, 1897)[12] was the most exhaustive, influential disquisition for many years.

Together with his private practice, he continued his clinical work at the Institute for Children's Diseases, enabling him to support his young family while he pursued his greater interest in clinical psychopathology through his practice with neurotic patients. We can see how many of his protean projects overlapped in time and how he had acquired analytical scientific reasoning, which he tried to apply to more subjective psychological investigations. But objective, measurable, and testable hypotheses were not the stuff of psychology, as its modern, often opaque jargon betrays.

With Josef Breuer, (1842-1925), also a former student of von Brücke, he explored the manifestations of hysteria. Breuer had treated the famous patient, Bertha Pappenheim—or 'Anna O', who suffered many hysterical symptoms. Instead of using Charcot's hypnosis they encouraged 'The talking cure' or 'chimney sweeping,' with abreaction, which seemed beneficial. They published their findings in *Studien über Hysterie* (1895) — the beginning of psychoanalysis. This was advanced in his *The Interpretation of Dreams* (1900), which although initially ignored, he thought his best book. He worked at intervals with Alfred Adler and C.G. Jung but neither could accept his notions of infantile sexuality, and they chose to pursue their studies independently. A massive literature[13] attests to his psychoanalytic theories: the notions of infantile sexuality, the interpretation of dreams, the id and ego principles, and other original concepts many of which have persisted in contemporary psychiatry and in daily language.[1]

I crave readers' indulgence if in what follows I speak of well known, admitted facts; the context necessitates this method. Freud's research in Neurology, mainly between 1882 and 1889 had yielded important results. Consequently he tried to find a physiological and materialist basis for his theories of the psyche,[14] but these of necessity were subjective. When Freud originated psychoanalysis he wanted it to be a science. In this he acknowledged that the neurological influence

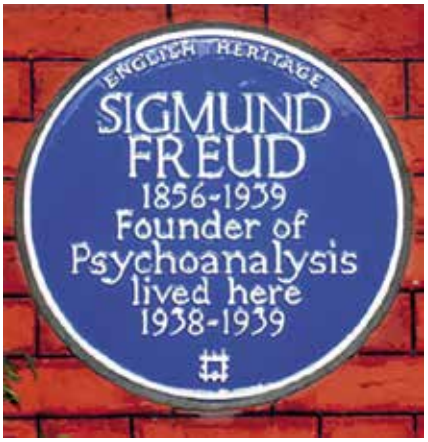

Figure 1. Freud blue plaque

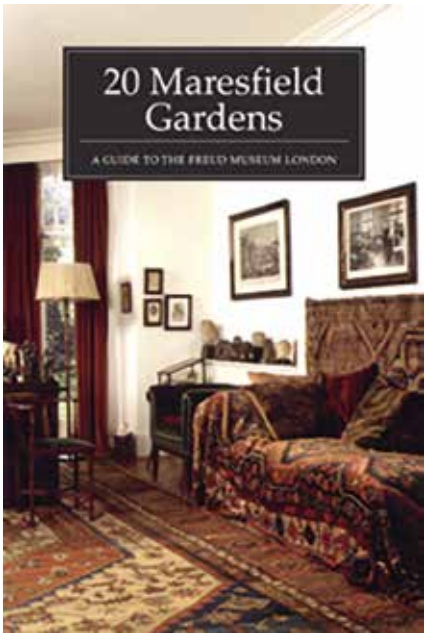

Figure 2. Freud's couch [Note picture of Charcot's demonstration above couch.]

Figure 3. 20 Maresfield Gardens, London
from https://londonist.com/2015/08/
five-things-you-have-to-see-at-the-freud-museum

of Brücke, Meinert and Charcot had coloured his subsequent thinking in his pioneering if controversial concepts in psychiatry.

Appraisal of psychoanalytic theory is beyond this author's expertise. The brilliant (not medically trained) scientist Medawar (1915-1987) maintained,[15] 'Doctrinaire psychoanalytic theory is the most stupendous intellectual confidence trick of the twentieth century.' And Tallis carpingly objected, 'The verdict has been uniformly [sic] negative: Freud as a scientist, metapsychologist, and diagnostician of society emerges as a quack.'[16] Despite such opprobrium, criticisms, and attempted refutations of Freud's work,[17] its spell remains powerful long after his death.[18] Psychoanalysis doubtless has theoretical and practical limitations. Freud exposed the flawed nature of human beings and their destructive conflict: no recipe for popularity. But his ideas were original, honest, brave and revolutionary. Validation of his scientific standing is shown by his election in old age as a Foreign Member of the Royal Society† on 25th June, 1936. His work in Neurology is unchallenged.

Disputes about religion, war and pacifism also occupied him. In a letter to Albert Einstein in the early 1930s, Freud observed that 'man has in him an active instinct for hatred and destruction.' He contrasted this 'instinct to destroy and kill' with an instinct 'to conserve and unify,' an instinct for love.

Biographical note

Freud was born to Jewish parents, Jacob and Amalie in May 1856 in Freiburg, Moravia, the first of seven children. In 1860 the family moved to Leopoldstadt in Vienna.[19]

Freud was a clever pupil at the local Gymnasium. From the age of eight he was reading Shakespeare and, despite the influence of an education in Greek and Latin, he later commented in a letter to Martha Bernays: 'I am taking up again the history of the island, the works of the men who were my real teachers all of them English or Scotch;' He began his studies in Medicine at Vienna University in 1873, graduating MD in 1881.

In Vienna he married Martha Bernays in 1886 and set up in private practice with neurotic patients and gradually developed his many controversial psychoanalytical theories, which were often traduced.[19]

When Hitler invaded Austria in 1938, Freud's many publications were burned, as the fruits of a 'Jewish science.' Like millions of Jews his family were persecuted, or murdered. Four of his sisters died in Nazi concentration camps. He was forced to flee to Britain in March 1938 where he spent his last days, still working, with his devoted daughter Anna at 20 Maresfield Gardens, London (Figures 2, 3). He surrounded himself by his collection of Roman fresco paintings, and sculpture, parts of mummy cases, paintings, treasured books on the cultures of Egypt, Greece and Rome, and his famous consulting couch.

In 1923, a diagnosis of verrucous squamous carcinoma of the palate had been made. He was subjected to over 30 operations by Hans Pichler (1877-1949) and an eminent Armenian American dentist, Varaztad Kazanjian (1879-1974), and endured a cumbersome prosthesis worn to replace his resected jaw and palate. Eventually, when yet another painful recurrence was deemed inoperable, with the agreement of Anna, he asked his friend Dr Max Schur (1897-1969), to administer morphine.[20] He died on September 23, 1939. His ashes were buried at Golders Green Crematorium.

Perhaps the last word on the integrity and legacy of Freud can be left to Albert Einstein after a long correspondence (Dec 1932):

> *"You have earned my gratitude and the grati- tude of all men for having devoted all your strength to the search for truth and for having shown the rarest courage in professing your convictions all your life."*

REFERENCES

1. McHenry LC. *Garrison's history of Neurology*. Springfield Illinois:Charles C Thomas. 1969;339-40,445,471-527.
2. Surbeck W, Killeen T, Vetter J, Hildebrandt G. *Sigmund Freud-early network theories of the brain.* Acta Neurochir. 2018;160:1235-1242. https://en.wikipedia.org/w/index.php?title=Sigmund_Freud_bibliography&oldid=831398475 (accessed May 14, 2018).
3. Triarhou LC1, Del Cerro M. *The histologist Sigmund Freud and the biology of intracellular motility.* Biol Cell. 1987;61(3):111-4.
4. Freud S. *Uber Spinalganglien und Ruckenmark des Petromyzon.* [On the Spinal Ganglia and Spinal Cord of the Petromyzon.] 1878.
5. Freud S. *Über den Bau der Nervenfasern und Nervenzellen beim Flusskrebs.* In: Sitzungsberichte der kaiserlichen Akademie der Wissenschaften. Wien Math Naturwiss Cl III Abt 1882;85:9-46. Cited by Florey E. In: K. Wiese Frontiers in Crustacean Neurobiology. Birkauser, 2013;4-6, 29.
6. Frixione E. *Sigmund Freud's Contribution to the History of the Neuronal Cytoskeleton.* Journal of the History of the Neurosciences 2003;12:12-24.
7. Freud S. *A new histological method for the study of nerve-tracts in the brain and spinal chord.* Brain 1884;7:86-88.
8. Pearce JMS. *Before Charcot.* In: Bogousslavsky J (ed): Hysteria The Rise of an Enigma. Front Neurol Neurosci. Basel, Karger, 2014;35:1-10.
9. Freud S. *On Aphasia: A critical study.* Stengel E (translator). New York: International Universities Press. Inc., 1953.
10. Freud S. *Letters of Sigmund Freud (1873-1939).* ed Freud E, Freud L. London. The Hogarth Press 1960
11. Pearce JMS. *Sigmund Freud, migraine and neurological work.* In: Fragments of Neurological History. London, Imperial College Press. 2003. Pp615-622.
12. Freud S. *Die Infantile Cerebrallähmung* (Infantile Cerebral Paralysis), Wie., Alfred Holder. 1897).
13. Freud S, Strachey J, Freud A. *Complete Psychological Works of Sigmund Freud.* Random House, 2001.
14. Bogousslavsky J. *Sigmund Freud's evolution from neurology to psychiatry: evidence from his La Salpêtrière library.* Neurology. 2011 Oct 4;77(14):1391-4.
15. Medawar PB. *Victims of psychiatry.* New York Review of Books 1975; Jan 23: 17.
16. Pearce JMS. *Sigmund Freud.* Lancet 1996;347:1039
17. Jay ME. Sigmund Freud. Encyclopædia Britannica, inc. May 04, 2018. https://www.britannica.com/biography/Sigmund-Freud. Access Date: May 13, 2018
18. Austin, Susan, '*Freud, Sigmund (1856-1939)*' Oxford Dictionary of National Biography, (Oxford: Oxford University Press, 2004).
19. Tallis RC. *Burying Freud.* Lancet 1996; 347: 667-69.
20. Schur M. *Freud: Living and dying.* New York: International Universities Press. 1972.

*Founder of the Anna Freud National Centre for Children and Families at Hampstead in 1952

†Proposers: W H Bragg; A V Hill; A C Seward; L N G Filon; A W Conway; G P Lenox-Conyngham; W H Eccles; Robert Robison; D L Chapman; J Gray; P P Laidlaw; E D Adrian; Wilfred Trotter; A D Hall; W Stiles

NICE dementia guideline /guidance updated

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

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

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NICE issued a guideline on dementia (hence-forward NG97) in June 2018,[1] updating the original guidance (sic) on this subject issued jointly with the Social Care Institute for Excellence in 2006.[2] NG97 is a substantial document, more than 400 pages in length, with 136 recommendations and 16 appendices. This reviewer admits to not having read every single page of this material (Appendix P alone runs to more than 600 pages, summarising an immense amount of data which might be profitably mined by others) – fortunately briefer summaries, of guidance, are available[3] – but has chosen to focus on those areas likely to be most pertinent to Neurologists with an interest in cognitive disorders, namely investigation (cognitive testing, imaging, biomarkers; Chapter 5) and treatment (dementia drugs, other medications; Chapters 11 and 14). (In the interests of full disclosure, it should be noted that a number of publications emanating from this reviewer's clinic are both included in and excluded from the guideline.) Specialists in other areas may wish to focus on other chapters, such as care planning, inpatient care, supporting informal carers, and staff training.

For cognitive testing in primary care, specific recommendations on suitable screening instruments are given (no similar recommendations are given for secondary care settings). The guideline advocates use of brief validated tools, the specified instruments being the 10-point cognitive screener (10-CS) and the six-item cognitive impairment test (6CIT). The former was unknown to me, and as far as I can ascertain there is only a single publication,[4] hence no validation in independent patient cohorts. 10-CS may indeed be a very good test (although NICE judge the index study to have an overall serious risk of bias) but pending further data it might be difficult to understand how it can be recommended, other than on the basis of opinion of what constitutes good practice.[5] The explanation relates to the committee's decision to base recommendations on the use of likelihood ratios (LRs), on which metric 10-CS scores highly (in the "very large increase in probability" range). Pragmatically, however, 10-CS has never been mentioned in referrals from primary care directed to this author's dedicated secondary care cognitive disorders clinic, unlike 6CIT which appears to be the most frequently used cognitive screening instrument in primary care in this catchment area, based on information contained in referral letters.[6] However, the negative scoring of 6CIT (higher scores worse) is associated, in our experience, with errors in scoring and reporting in about a quarter of referrals from primary care.[6] The guideline finds no place for the General Practitioner Assessment of Cognition (GPCOG), apparently due to lack of data (p103), other than to acknowledge it as the most cost effective when compared to MMSE and 6CIT (p95). Other systematic reviews have preferred GPCOG because it assesses recall and visuospatial skills, and incorporates an informant interview;[7] it is frequently mentioned in referrals from primary care to our clinic, as is the MMSE.[6] MoCA is reported to be "not well tolerated by people with suspected dementia" (p100), but TYM is recommended (p110) despite both cited studies emanating from secondary care settings. Longer (i.e. more time consuming) tests "did not appear to be more effective at detecting dementia than shorter and simpler tests" (p102); although this generalisation may be true in primary care, there is some evidence to the contrary in secondary care.[8]

For imaging, functional studies with FDG-PET or SPECT are advocated in suspected Alzheimer's disease and frontotemporal dementia undiagnosed by other methods, although neither achieved very large LRs, and FP-CIT-SPECT or MIBG cardiac scintigraphy for suspected dementia with Lewy bodies. Specialist input to interpret imaging data is recommended. Concerning biomarkers, amyloid PET is not discussed (but is one of the research recommendations, p113) but CSF biomarker studies are recommended in suspected Alzheimer's disease although again the LRs were not spectacular.

Guidelines for treatment with cholinesterase inhibitors and memantine have been updated, and generally speaking these are more liberal/less restrictive than previous documents from NICE, but whether this is a consequence of evidence or cost (a previous concern of one senior committee member[9]) is less apparent to this reviewer: "if cost containment had been a motivating factor in restricting prescribing to people with specialist experience of Alzheimer's disease, this was no longer such a substantial concern" (p197) because all the drugs have switched from proprietary to generic status. Hence, with a recommendation from a specialist, memantine may now be started in primary care. Furthermore, slavish adherence to MMSE scores to determine prescription decisions is now eschewed: "health professionals should not rely solely on cognition scores" (p198), and the importance of considering the "overall benefit of treatment" (p211) is emphasised. A corollary is that disease severity should not be used as a reason for drug discontinuation (p212).

The recommendations on antipsychotics for dementia-associated agitation, aggression, distress and psychosis are familiar i.e. avoid if at all possible. For depression psychological treatments are to be considered, and antidepressants should not be routinely offered. For sleep problems, a significant issue, especially for many carers, melatonin is firmly vetoed (p323), despite a recent more positive meta-analysis which is not cited.[10]

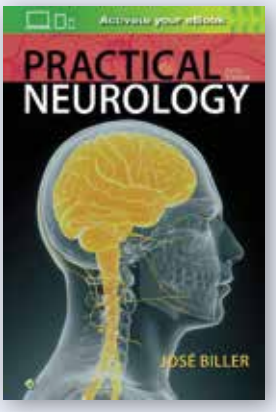
Overall, these guidelines are to be welcomed. The committee is to be congratulated on the immense amount of work and analysis which has evidently gone in to their deliberations. Elements in the original guidance which were viewed as tendentious and provoked objection (e.g. single point of referral omitting any substantive role for Neurologists, a "one size fits all" approach)[11] not least in the pages of this journal,[12] are no longer in evidence – whether this reflects the inclusion of a (co-opted) Neurologist on the committee is uncertain, but if so, take a bow Dr Jeremy Isaacs!

What will be the effect of these guidelines? Will they have any impact on practice? Experience with the previous guidance suggests that they may attract plenty of commentary, but little by way of analysis of actual effects.[13,14] If NICE guidelines, adoption of which is often de facto mandatory rather than optional (hence a possible Orwellian use of language), are considered as interventions, then their effects should surely merit some kind of evaluation as for any other clinical intervention. For example, it would have been interesting to research how many people were harmed, or what additional costs were incurred (e.g. for nursing home placement), by previous NICE guidance restricting use of cholinesterase inhibitors.

REFERENCES

1. National Institute for Health and Care Excellence. *Dementia. Assessment, management and support for people living with dementia and their carers.* NICE Guideline 97. Methods, evidence and recommendations. London: NICE, 2018(https://www.nice.org.uk/guidance/ng97).
2. National Institute for Health and Clinical Excellence/Social Care Institute for Excellence. *Dementia: supporting people with dementia and their carers in health and social care.* NICE Clinical Guidance 42. London: NICE, 2006.
3. Pink J, O'Brien J, Robinson L, Longson D, on behalf of the Guideline Committee. *Dementia: assessment, management, and support: summary of updated NICE guidance.* BMJ 2018;361:k2438.
4. Apolinario D, Lichtenthaler DG, Magaldi RM et al. *Using temporal orientation, category fluency, and word recall for detecting cognitive impairment: the 10-point cognitive screener (10-CS).* Int J Geriatr Psychiatry 2016;31:4-12.
5. Larner AJ. *Re: Dementia: assessment, management, and support: summary of updated NICE guidance.* https://www.bmj.com/content/361/bmj.k2438/rr-0 (19 July 2018).
6. Cannon P, Larner AJ. *Errors in the scoring and reporting of cognitive screening instruments administered in primary care.* Neurodegener Dis Manag 2016;6:271-276.
7. Creavin S, Wisniewski S, Noel-Storr A et al. *Cognitive tests to help diagnose dementia in symptomatic people in primary care and the community.* Br J Gen Pract 2018;68:149-150.
8. Larner AJ. *Performance-based cognitive screening instruments: an extended analysis of the time versus accuracy trade-off.* Diagnostics (Basel) 2015;5:504-512.
9. O'Brien JT. *NICE and anti-dementia drugs: a triumph of health economics over clinical wisdom?* Lancet Neurol 2006;5:994-996.
10. Wang YY, Zheng W, Ng CH, Ungyari GS, Wei W, Xiang YT. *Meta-analysis of randomized, double-blind, placebo-controlled trials of melatonin in Alzheimer's disease.* Int J Geriatr Psychiatry 2017;32:50-57.
11. Larner AJ. *Integrated care pathways in dementia: a challenge to National Institute for Health and Clinical Excellence/Social Care Institute for Excellence guidance.* J Integrated Care Pathways 2007;11:95-99.
12. Doran M, Larner AJ. *NICE/SCIE dementia guidance: time to reconsider.* Adv Clin Neurosci Rehabil 2008;8(1):34-35.
13. Larner AJ. *Impact of the National Institute for Health and Clinical Excellence and Social Care Institute for Excellence's dementia guidelines in a neurology-led memory clinic.* Clin Med 2009;9:197-198.
14. Menon R, Larner AJ. *Use of cognitive screening instruments in primary care: the impact of national dementia directives (NICE/SCIE, National Dementia Strategy).* Fam Pract 2011;28:272-276.

Practical Neurology 5th Edition



Editor: Jose Bille
Published by: Wolters Kluwer
Pages: 962
ISBN: 9781496326959

Reviewed by:
Dr Jeff Cochius, Consultant Neurologist, Senior Lecturer (hon.), Clinical Neurosciences Directorate, Dept. of Neurology, Norfolk & Norwich University NHS FT & University of East Anglia, UEA, Norwich, UK.

Dr Ekkehart F.A. Staufenberg, Consultant Neuropsychiatrist, Clinical Neurosciences Directorate, Dept. of Neurology, Norwich Epilepsy & VNS Implantation Centre Clinic, Norfolk & Norwich University NHS FT.

Dr Mary Nichols, General Practitioner, HMP Wayland, Griston, Norfolk, UK.

Jose Biller's 63 chapters multi-author Practical Neurology 5th Edition paperback, separate eBook, and on-line videos provides a didactic two part overview of neurological disorders, using both overview and more in-depth information.

In Section 1, concerning Diagnosis, Chapters 1-39 are all entitled: 'Approach to the Patient with…..'. Taking a patient's key presenting neurological problem allows the clinician to access topics which include acute confusional state, neurocognitive disorders, headache, seizures, dizziness and vertigo, muscle weakness, movement disorders, functional disorders, neuroimaging, paediatric neurology (chapters 37 & 38), and sleep disorders. Pictures and plates illustrate specific findings, and cross-reference to the e-Book and video library. However, individual chapters' content lacks a similarly harmonising editorial structure and this reduces the book's user-friendliness. Knowing where on the page to direct one's gaze can be very helpful for primary care practitioners, referring to a text while consulting. The same probably applies to specialist clinicians wishing to find detail in an area of practice they rarely encounter, though they may be less likely to have access to their library while consulting, and may also be less willing to dip into their books at the time!

The quality of the information available in Practical Neurology is generally high but rigour is impaired in places by lack of reference to published international consensus documents. For instance, the International League Against Epilepsy's (ILAE; April 2017) diagnostic guidelines for seizures and epilepsies, now part of ICD11 (draft, WHO 2018), was published well before this volume. This is an omission which, perhaps, might have been avoided, especially as the compendium is not likely to be revised again for several years.

The volume's second section, concerning treatment, has twenty-four chapters with a new set of authors from the first section. The topics here are mainly pathophysiological but sometimes refer to the anatomical site of disease or to a patient group. Headings include vascular/haemodynamic-, movement-, children's and adult epilepsies (two separate chapters), pain (two separate chapters), AIDS related -, central-, peripheral- as well as metabolic neurological disorders. There is overlap with Section 1, which is probably inevitable. Conversely, there was under emphasis of concerns about certain prescription medicines, such as opioids.

Practical Neurology is not intended to replace more comprehensive reference texts for Neurology. The didactic 'presenting complaints' approach remains too inclusive to permit easy access to its wealth of information. For most general practitioners, the detail is too much for everyday use, although practitioners with a special interest in Neurology or an area of Neurology will find certain chapters very useful. Neurologists working mostly in a subspecialist field may find the book useful when encountering another sub-speciality. Non-Neurologists required sometimes to make decisions in neurological differential diagnosis might also benefit, and improve their effectiveness in collaborating with Neurology.

This valuable text certainly deserves to appear as a further, 6th, edition. We suggest that such a work would benefit from somewhat more diligent adherence to recent international consensus on diagnostic terminology. Furthermore, adding to the 63 chapters to rectify the current paucity of Behavioural Neurology and (co-morbid) neuropsychiatric coverage, would do full justice to a readership of the 2020s.

Nada El Youssef,
MD, is a Senior Neurology Registrar at Saint Georges University Medical Center, Beirut, Lebanon.

Mounir Khoury,
MD, is a former head of the Division of Neurology (2010-2017), a Consultant Neurologist and Assistant Professor at Saint George Hospital University Medical Center in Lebanon and a Lecturer at the University of Balamand. He trained at Beaujon Hospital, Paris, France and Saint Joseph University, Beirut, Lebanon and graduated from Paris Descartes University, France.

Joseph Saade,
MD, is a Junior Neurology Registrar at Saint George Hospital University Medical Center, Beirut, Lebanon.

Aline Mourad,
MD, is a Consultant Neurologist, Assistant Professor at Saint George Hospital University Medical Center in Lebanon and a Lecturer at the University of Balamand. She trained at Lariboisiere Hospital in Paris and graduated from Paris 7 University, France. She has a wspecial interest in neurovascular disorders and is a member of the French neurovascular society.

Nancy Maalouf,
MD, is a Consultant Neurologist and Assistant Professor at Saint George Hospital University Medical Center in Lebanon and a lecturer at the University of Balamand. She trained at the University of Arkansas for Medical Sciences Medical Center and is Board certified by the American Board of Psychiatry and Neurology.

Correspondence to:
Nada El Youssef
Email: nadaelyoussef@gmail.com

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Homonymous hemianopia as presenting symptom of Multiple Sclerosis

Abstract:
Multiple Sclerosis can present with various clinical manifestations depending on the anatomical location of the demyelinating lesions. We report the case of a 48 year old woman who complained of blurred vision. Her examination documented a right homonymous hemianopia which had resulted from an active demyelinating lesion located at the origin of the left optic radiation. A first attack of multiple sclerosis was diagnosed. This case highlights the importance of a workup for demyelinating diseases in the setting of any visual dysfunction.

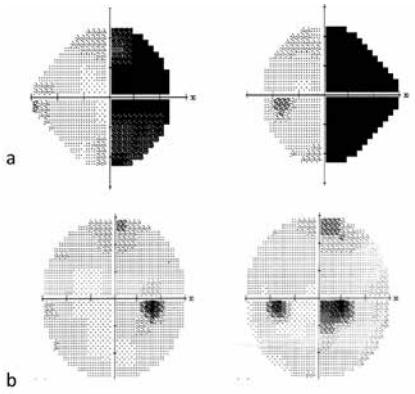


Figure 1 (a): Humphrey visual field showing a complete right homonymous hemianopia at the beginning of the reported symptoms and 1 month later (b), with near complete resolution of the visual field defect.

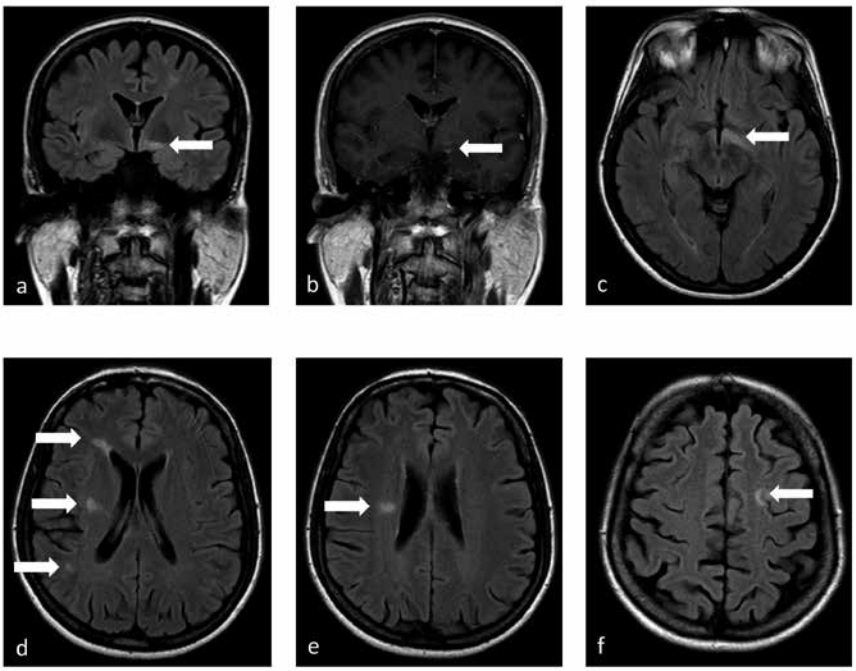
Introduction

Multiple Sclerosis (MS) clinical manifestations are diverse and depend on the part of the central nervous system involved in the disease.[1] Ophthalmic symptoms are commonly related to optic neuritis while homonymous hemianopia is a rare presentation.[2] We report the case of a 48 year old woman who presented with right homonymous hemianopia as initial manifestation of MS.

Case report

A 48-year-old woman with diabetes mellitus type 2 on metformin, presented to the ophthalmology clinic with a two-week history of binocular blurred vision. One week prior to presentation, she started seeing black spots in her right visual field. These visual symptoms were worsening gradually. Visual fields revealed a right homonymous hemianopia (Figure 1, a), so she was referred to the neurology department for admission. Patient denied any previous history of headache,

Figure 2: (a- arrow) hyperintense lesion on coronal T2 FLAIR sequence at the level of the left fornix, posterior to the left optic tract, showing enhancement after injection of gadolinium (b- arrow). Axial T2 FLAIR sequence showing the same lesion (c- arrow). Multiple hyperintense lesions on T2 FLAIR sequence located in the periventricular, subcortical and juxtacortical areas (d, e, f- arrows).



sensory/motor deficit, visual, speech or gait disturbances. Neurological examination was unrevealing except for a right homonymous hemianopia.

Brain MRI showed multiple lesions that are hyperintense on T2/FLAIR and hypointense on T1 sequences located in the subcortical, periventricular, and right thalamic areas, with one enhancing lesion within the left fornix posterior to the left optic tract (Figure 2). Cervico-dorsal spine MRI was normal. Serological work up including ESR, ANA, and ACE was unremarkable. Cerebrospinal fluid analysis showed 6 white blood cells, a protein level of 42mg/dL, a glucose level of 80mg/dL, positive oligoclonal bands and an IgG index of 1.19.

A diagnosis of relapsing remitting MS was established based on the 2017 McDonald criteria. During her hospital stay, the patient received 1g of intravenous methylprednisolone daily for five consecutive days with partial recovery of her visual deficit. Teriflunomide was initiated at a dose of 14mg daily upon discharge.

Follow up visual field testing one month after discharge revealed partial improvement in the right homonymous hemianopia (Figure 1, b).

Discussion

Multiple sclerosis is a chronic, immune-mediated, demyelinating disorder of the central nervous system.[1] Early diagnosis is important since multiple disease modifying agents are now widely available.[3]

Common anatomical locations of symptomatic MS lesions include the optic nerve causing monocular visual loss, the spine resulting in limb weakness or sensory anomalies, the brainstem with subsequent double vision, and the cerebellum leading to ataxia.[1] On the other hand, unusual presentations of MS include pain syndromes, cranial nerve abnormalities, movement disorders, paroxysmal symptoms, and homonymous hemianopia,[4] the latter being reported in only 0.5%–3.5% of cases.[2] More frequently, homonymous hemianopia result from a stroke (69.6%), trauma (13.6%), tumour (11.3%) or brain surgery (2.4%).[5]

Recovery from homonymous hemianopia secondary to a demyelinating process like MS usually carries a favourable prognosis,[6] as seen in our case, where near complete recovery of visual field defect was documented as early as one month after discharge. While in cases of stroke, the recovery is usually partial and requires rehabilitative techniques.[7]

This case describes a rare initial presentation of MS with homonymous hemianopia related to an enhancing demyelinating lesion located at the origin of the left optic radiation. It also highlights an important reminder that patients may subjectively report homonymous hemianopia as blurred vision.

REFERENCES

1. Brownlee WJ, Hardy TA, Fazekas F, et al. *Diagnosis of multiple sclerosis: progress and challenges.* Lancet 2017; 389: 1336-46.
2. Frederiksen JL, Larsson HBW, Nordenbo AM, et al. *Plaques causing hemianopsia or quadrantanopsia in multiple sclerosis identified by MRI and VEP.* Acta Ophthalmol 1991; 69: 169–177.
3. Reich D, Lucchinetti C, Calabresi P. *Multiple Sclerosis, review article.* N Engl J Med 378; 2 nejm.org January 11, 2018.
4. Evlice A, Demir T, Kaleagası C, et al. *Rare onset symptoms in multiple sclerosis.* Acta Clinica Belgica 2016, 71:3, 154-157, DOI: 10.1080/17843286.2016.1147675.
5. Zhang X, Kedar S, Lynn M.J, et al. *Homonymous hemianopias Clinical–anatomic correlations in 904 cases.* Neurology 2006; 66; 906-910 DOI 10.1212/01.wnl.0000203913.12088.93.
6. Plant GT, Kermode AG, Turano G, et al. *Symptomatic retrochiasmal lesions in multiple sclerosis: Clinical features, visual evoked potentials, and magnetic resonance imaging.* Neurology 1992; 42:68–76.
7. Perez C and Chokron S. *Rehabilitation of homonymous hemianopia: insight into blind sight.* Front.Integr.Neurosci. (2014) 8:82. doi: 10.3389/fnint.2014.00082.

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DECEMBER

Encephalitis Silver Jubilee PhD Fellowship 2019
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Academic institution sought to host the 2019 Encephalitis Society PhD Fellowship.
T. 01653 692583
E. admin@encephalitis.info
www.encephalitis.info/phd2019

2019

JANUARY

2nd International Conference on Microbiota-Gut-Brain Axis
17-18 January, 2019; Amsterdam, The Netherlands
www.mindmoodmicrobes.org/index.php

17th Annual King's Neuromuscular Symposium
25 January, 2019; London, UK
E. knmsymp@gmail.com
https://bit.ly/2BscMS5

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Gliomas /TYA Tumours
31 January, 2019; NHNN, London
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/neurooncology

FEBRUARY

Symposium: Living with Cognitive Disability
1 February, 2019; UCL, Queen Square, London, UK
https://onlinestore.ucl.ac.uk
(search F82 UCLP CNR)
E. cnr@ucl.ac.uk

The Society for Research in Rehabilitation Winter Conference 2019
5 February, 2019; Nottingham, UK
www.srr.org.uk

Dementias 2019
10% discount for ACNR readers, quote: 10ACNR
14-15 February, 2019; London, UK
www.dementiasconference.com
T. 020 7501 6761

MARCH

Neurology 2019
1 March, 2019; Royal College of Physicians of Glasgow, UK
T. Hanne Wylie – 0141 221 6072,
E. Hanne.Wylie@rcpsg.ac.uk

TNA Study Day for Healthcare Professionals 2019
2 March, 2019; Birmingham, UK
E. admin@tna.org.uk

The BNPA Annual Meeting
7-8 March, 2019; London, UK
www.bnpa.org.uk
T. 020 89876111
E. hello@bnpa.org.uk

BPNS Teaching Course on Peripheral Neuropathy
14 March, 2019; Bristol, UK
www.bpns.org.uk
E. secretariat@bpns.org.uk

Hypnotherapy in neurological and other medical clinical settings
15 March, 2019; Stoke-on-Trent, UK
https://www.bscah.com/book-event/hypnosis-inneurologicalandothermedical clinicalsettings

MS Foundation MasterClass
20-22 March 2019; Halifax Hall, Sheffield, UK
https://multiplesclerosisacademy.org/events/ms-foundation-masterclass-7-module-1

European NeuroConvention 2019 – In partnership with ACNR
26-27 March 2019; Birmingham, UK
FREE tickets: https://bit.ly/2rqwkjX

Naidex 2019
26-27 March 2019; Birmingham, UK
www.naidex.co.uk

AD/PD 2019
26-31 March; 2019; Lisbon, Portugal
www.adpd.kenes.com

Sleep Medicine 2019
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www.mahealthcareevents.co.uk
T. 020 7501 6761

Neurology 2019: leading edge neurology for the practising clinician
28-29 March, 2019; Institute of Education, London, UK
https://bit.ly/2ScsN3W

APRIL

Biomarkers in Neurodegenerative Diseases
2-5 April, 2019; UCL, Queen Square, London
E. r.paterson@ucl.ac.uk
https://bit.ly/2P5JbS1

The London-Innsbruck Colloquia on Status Epilepticus and Acute Seizures
7-9 April, 2019; London, UK
www.statusepilepticus.eu

International Congress on Neuropathic Pain (NeuPSIG)
9-11 May, 2019; London, UK
www.iasp-pain.org
E. IASPDesk@iasp-pain.org

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Benign & Metastatic Tumours
11 April, 2019; NHNN, London
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/neurooncology

JUNE

Matthew's Friends KetoCollege
4-6 June, 2019; East Grinstead, UK
www.mfclinics.com/keto-college
E. ketocollege@mfclinics.com

MS Intermediate MasterClass
12-14 June 2019; Halifax Hall, Sheffield, UK
https://multiplesclerosisacademy.org/events/ms-intermediate-masterclass-8-module-1/

Parkinson's Academy: Parkinson's Advanced MasterClass
18-20 June 2019: Halifax Hall, Sheffield, UK
https://parkinsonsacademy.co/events/parkinsons-advanced-masterclass-36a-module-1

The 5th EAN: Neuroinflammation – Science. Synergies. Solutions.
29 June – 2 July, 2019
www.ean.org/Oslo2019

JULY

The 2nd Queen Square Multidisciplinary Neuro-Oncology Course: Neurotoxicity, Late effects, Rehabilitation & Ethics
11 July, 2019; NHNN, London
E. jeremy.rees@ucl.ac.uk
www.ucl.ac.uk/ion/education/courses/other/neurooncology

SEPTEMBER

Parkinson's Academy: Parkinson's Foundation Masterclass
19-20 September 2019; Halifax Hall, Sheffield, UK
https://parkinsonsacademy.co/events/parkinsons-foundation-masterclass-37f

OCTOBER

Joint meeting of the Society for Research in Rehabilitation and the British Society of Rehabilitation Medicine
14-15 Oct 2019, 2019; University of Warwick, UK
www.srr.org.uk

NOVEMBER

MS Academy: MSologists MasterClass
6-8 November 2019; Halifax Hall, Sheffield, UK
https://multiplesclerosisacademy.org/events/msologists-masterclass-9-module-1

Functional Strokes – Rehabilitation Can hypnotic (and allied) techniques help?

Conference details: 11th October, 2018, Edinburgh, Scotland. ***Report by:*** Dr Ann Williamson, BSCAH. www.bscah.com
Conflict of interest statement: None declared.

If you thought functional neurological disorders were all in the mind or restricted to those people with emotional difficulties then this meeting would have soon altered your perceptions.

Professor Jon Stone started the day by talking about the diagnostic techniques, aetiology and treatment of Functional Motor Disorders. Rather than being a diagnosis formed by exclusion, Professor Stone showed that there are positive diagnostic signs of a functional disorder. Rather than being 'all in the mind', they are a disorder of function that may have a variety of psychogenic underpinnings and sometimes no obvious emotional or traumatic trigger. Functional Disorders are something that all humans experience to a greater or lesser extent, from such things as a tension headache to irritable bowel syndrome or functional stroke. Functional Neurological Disorders 'are no longer assumed to be only the result of 'conversion' of psychological conflict but now understood as a complex interplay between physiological stimulus, expectation, learning and attention.... with biopsychosocial predisposing, triggering and perpetuating inputs'.[1]

Dr Ranjan Sanyal, a Consultant Stroke Physician, University Hospitals of North Midlands then described how he uses hypnosis with functional strokes. Functional disorders are very common and are responsible not only for a large amount of human suffering, but also a huge cost to the economy of over £14 billion.[2] 8.4% of all strokes are functional and the condition can be as debilitating as Parkinson's or Multiple Sclerosis. Dr Sanyal described how he uses hypnosis very successfully with his patients, building rapport, using imagery, and giving appropriate suggestions in hypnosis.

Dr Alastair Dobbin then talked about how positive and negative episodic memories that lie outside of conscious awareness can influence our feelings of autonomy, competence and relatedness. Someone with resilience has rapid access to positive emotions which speeds recovery from a threat, so our therapies should seed or prime a growth or recovery model in our patients.

Pauline Halliday, an Occupational Therapist and a Clinical Specialist in stroke, then gave a presentation as to how she used hypnosis to help a 'difficult' stroke patient with 'functional overlay'. By means of a simple breathing induction and using imagery of a safe, calm place and a beach, that the patient could go to in her imagination, her agitation and anxiety were reduced. She was taught how to use this whenever she wanted to feel calmer. This also improved her sleep pattern.

Pauline also uses hypnosis with patients with Thalamic or Central Pain Syndrome using the patient's metaphors in hypnosis to help a change in perception (switches, water, warmth etc.) with a resultant reduction in analgesic medication. She has also used hypnosis successfully to manage fear of going into the MRI Scanner, during Carotid Endarterectomy, with Functional Stroke (mainly with vocal dysfunction), and generalised anxiety.

After lunch, Dr Jason Price, a prominent Consultant Neuropsychologist from South Tees Hospital NHS Trust talked about how the profile of hypnosis in the NHS suffers from 'alternative therapy' perception. Far from being an 'alternative therapy' Dr Price argues, hypnosis sits comfortably within the '3rd Wave' cognitive therapies such as Mindfulness, Acceptance and Commitment Therapy, Compassion Focused Therapy, DBT and Transdiagnostic Therapy. There is also good evidence of 'added value' of hypnosis with other 'mainstream' therapies. He pointed out the importance of imagery, not only in hypnosis but also within these other therapeutic approaches. It works in a primary modality and is very powerful in re-scripting/ cognitive restructuring in trauma work.[3] Visual Imagery is recommended for post-stroke limb movement recovery (National Clinical Guideline for Stroke 5th edition, 2016) and there are similarities, as well as some differences between hypnosis and mindfulness[4,5] and hypnosis and EMDR.[6] Hypnosis can both reproduce and remove functional symptoms, 'turn off' the neural circuits involved in agency, the executive processes involved in self-monitoring and automatic neuropsychological processes.[7] With EEG and fMRI evidence the development of cognitive neuroscientific understanding of hypnosis has developed alongside contemporary cognitive neuroscience understanding of Functional Neurological Disorders.[8-11]

Dr Paul Molyneux, a Consultant Neurologist from West Suffolk Hospital Trust and Addenbrookes, then reported how he uses hypnosis within an out-patient department treating Non-Epileptic Seizures and migraine. In a busy clinic there is very little time to make a diagnosis let alone treat the condition but informal hypnotic techniques can help. This involves using reflective listening, with attention to body language, confirming and explaining the diagnosis while building rapport, together with the careful use of language and metaphor, especially when breaking the diagnosis of Non-Epileptic Seizures.[12] He stressed the importance of touch and giving reassurance by physical examination and then using a simple hypnotic induction to increase the effectiveness of the positive suggestions given. Dr Molyneux also described how he uses hypnosis and metaphorical imagery to help patients with migraines. Self-hypnosis gives the patient a life long tool.

This was followed by Devin Terhune from Goldsmith's University of London describing his recent meta-analysis of hypnotic suggestibility in functional and dissociative disorders which support an increased hypnotic susceptibility. The limitations of methodology give rise to a weak scientific evidence base despite the fact that patients and doctors find hypnosis helpful and empowering.

The final presentation of the day was given by Professor Charles Warlow, Emeritus Professor of Medical Neurology at Western General Hospital, summarising why hypnosis has been underutilised in the past and how it could be used in the future.

A most fascinating day was ended by a general panel discussion between the presenters and the audience on the way forward for hypnosis in the management of Functional Neurological Disorders.

References

1. *Complex regional pain syndrome and functional neurological disorders: time for reconciliation.* Popkirov S, Hoeritzauer I, Colvin L, Carson A & Stone J (2018) Journal of Neurology, Neurosurgery & Psychiatry. Published Online First: 24 October 2018. doi: 10.1136/jnnp-2018-318298
2. *The cost of somatisation among the working-age population in England for the year 2008–2009.* (2010) Bermingham S, Cohen A, Hague J & Parsonage M. Mental Health in Family Medicine. Vol 7(2): 71–84.
3. *Imagery re-scripting and reprocessing therapy after failed prolonged exposure for post-traumatic stress disorder following industrial injury.* (2007) Grunert B K, Weis J M, Smucker M R, Christianson H F. Journal of Behaviour Therapy & Experimental Psychiatry. Vol 38 (4) 317-28.
4. *Do Hypnosis and Mindfulness Practices Inhabit a Common Domain? Implications for Research, Clinical Practice, and Forensic Science.* (2012) Lynn S, Malaktaris A, Maxwell R, Mellinger D & van der Kloet D. Journal of Mind-Body Regulation. Vol 2 (1) 12-26
5. *Metacognition of intentions in mindfulness and hypnosis.* (2016) Lush P, Naish P & Dienes Z. Neuroscience of Consciousness. Volume 2016, Issue 1, 1 January 2016
6. *Introduction to the Special Section: Hypnosis and EMDR.* (2001) Frischholz J, Kowal J & Hammond, D. The American Journal of Clinical Hypnosis. Vol 43(3-4) 179-182
7. *Hypnosis as therapy for functional neurologic disorders.* (2017) Deeley Q. Handbook of Clinical Neurology. Vol 139, 585-595
8. *Brain Activity and Functional Connectivity Associated with Hypnosis.* (2017) Jiang H, White M, Greicius M, Waelde L & Spiegel D. Cerebral Cortex. Vol 27 (8) 4083-4093.
9. *Neuro-hypnotism: prospects for hypnosis and neuroscience.* (2013) Kihlstrom J. Cortex. Vol 49 (2) 365-74.
10. *Hypnotic induction is followed by state-like changes in the organization of EEG functional connectivity in the theta and beta frequency bands in high-hypnotically susceptible individuals.* (2014) Jamieson G & Burgess A. Frontiers in Human Neuroscience 2014 (8) 528.
11. *Improving working memory performance in brain-injured patients using hypnotic suggestion.* (2017) Lindeløv J, Overgaard R & Overgaard M. Brain. Vol 140 (4) 1100-1106.
12. *Acceptability and effectiveness of a strategy for the communication of the diagnosis of psychogenic nonepileptic seizures.* (2010) Hall-Patch L, Brown R, House A, Howlett S, Kemp S, Lawton G, Mayor R, Smith P, Reuber M; NEST collaborators. Epilepsia. Vol 51(1) 70-8.

THE 7TH LONDON-INNSBRUCK COLLOQUIUM ON STATUS EPILEPTICUS AND ACUTE SEIZURES

7-9 April, 2019: The Francis Crick Institute, London, UK

Programme

- Nobel Laureate lecture
- 10 sessions covering a range of clinical areas and a faculty of leading international figures from 15 countries
- 2 'Data Blitz' sessions with new work presented in quick-fire 6 minute segments
- 3 workshops: clinical research & orphan conditions; outcomes of status epilepticus; status epilepticus due to nerve gases/poisons
- 2 satellite sessions
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Colloquium organised by Professors Simon Shorvon, Eugen Trinka and Matthew Walker, under the patronage of the ILAE (British Branch), UCL Queen Square Institute of Neurology, and Paracelsus Medical University of Salzburg.

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http://www.ucl.ac.uk/ion/education/courses/other/neurology

Faculty of Neuropsychiatry Annual Conference

Conference details: 13th-14th September, 2018, Royal College of Psychiatrists, London, UK. ***Report by:*** Dr George El-Nimr, Consultant Neuropsychiatrist, Academic Secretary of Faculty of Neuropsychiatry, Royal College of Psychiatrists. ***Conflict of interest statement:*** None declared.

Over two days, the Faculty hosted an unprecedented number of over 400 delegates from approximately 12 countries. With a host of distinguished speakers and a range of session formats, the conference covered important clinical and research topics.

Professor Burn, our College President, opened the conference with an update on the College's Neuroscience Project, which was followed by a dedicated session on 'Neurosciences for Psychiatrists', covering important areas in Neuroanatomy, Neurophysiology and Neuroimaging.

Dr Paul Johns, Consultant Neuropathologist and Senior Lecturer in Neuroanatomy at St George's Hospital in South London, discussed the functional anatomy of the human Amygdala, including how the Amygdala is involved in implicit learning and its implication in a wide range of neuropsychiatric conditions, such as anxiety, depression, phobias and post-traumatic stress disorder. Neurophysiology in a mental health setting was then explored by Dr Nandini Mullatti.

Dr Oliver Robinson, who runs the Anxiety Lab within the Neuroscience and Mental Health Group at the Institute of Cognitive Neuroscience, University College London, subsequently provided a historical overview of the last 30 years of neuroimaging in anxiety disorders. Attempts to develop new treatments such as deep brain stimulation on the back of some of the early work were discussed.

A lively discussion around the conceptions of the Mind and various proposed models was certainly one of the conference highlights. Professor Cavanna of the University of Birmingham presented an overview of the clinical interface between neurology and psychiatry and how this is illustrated in the behavioural symptoms caused by neuropsychiatric conditions.

In an interesting talk entitled 'Delusion and rationality', Lisa Bortolotti, Professor of Philosophy at the University of Birmingham, discussed how understanding the origins of delusions can enhance our insight into their psychopathology and potentially inform the treatment plan. Professor Karl Friston offered a highly regarded session on the computational psychiatry of psychosis. The talk utilised schizophrenia as a case study for this approach.

The concept of 'Neuro-Dogma' was challenged in the context of our medical humanities session. Following an introduction on 'Neuro-culture' by Dr Ken Barrett, internationally renowned Professor Andrew Lees presented an overview of his book 'Mentored by a Madman'. This was followed by a short critique of 'neuro-mania' by Professor Ray Tallis.

The conference also explored the challenges around the diagnosis and management of Frontal Lobe Seizures. Aspects such as the semiology and genetics of frontal seizures and differential diagnosis with parasomnias were discussed by Dr Aileen McGronigal, Professor Zuberi and Dr Chris Derry.

The growing interest in Functional Neurological Disorder, its clinical aspects and service challenges prompted a dedicated plenary session that was chaired by Dr Nick Medford, who also contributed to the discussion with a talk on multidisciplinary inpatient treatment. Functional cognitive disorders were covered by Dr Stoyan Popkirov. Various overlapping clinical syndromes were discussed, alongside underlying mechanisms and diagnostic features. Service development issues in this particular respect were explored by Professor Mark Edwards.

A carer, who is professionally also deeply immersed in the world of Neuroscience, talked about Brain Injury as a family affair and the gap between the Neuropsychiatric sequelae of Brain Injury as presented in academia and what actually happens within families behind closed doors.

As always, our interactive seminars covered various clinical, legal and research topics addressing a wide range of educational needs in a format that has always been highly valued by delegates. These included topics such as brain injury in the court of protection, motion and emotion across the lifespan and medicine and psychology in managing challenging behaviour after brain injury. Other sessions in the second day programme included assessing and treating circadian rhythm disorders, how flying affects the brain and 'funny turns; relevance to psychiatry'.

As in previous years, the conference offered a platform for trainees to present their work in poster as well as oral format. Trainees were encouraged through recognition and award schemes.

The next conference for the Faculty of Neuropsychiatry is scheduled for 19 and 20 September 2019. As the programme is being developed, the Faculty would certainly welcome any suggestions or contributions from colleagues; please forward any proposals to Emma.George@rcpsych.ac.uk

A lively discussion around the conceptions of the Mind and various proposed models was certainly one of the conference highlights.

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UKABIF's 10th Annual Conference 2018

Conference details: 5th November, 2018, London, UK. ***Report by***: Louise Blakeborough MSc on behalf of UKABIF. ***Conflict of interest statement:*** None declared.

Dr Andrew Bateman, Chair of the United Kingdom Acquired Brain Injury Forum (UKABIF), welcomed delegates to the organisation's 10th Annual and 20th Anniversary Conference, held this month at the Royal Society of Medicine in London. The conference programme reflected the issues outlined in the recently published report by the All-Party Parliamentary Group (APPG) on Acquired Brain injury (ABI) entitled 'Acquired Brain Injury and Neurorehabilitation: Time for Change'.

The development and future of specialised neurorehabilitation was discussed by Colonel Alan Mistlin, Chair of the Clinical Reference Group for Rehabilitation and Disability. Neurorehabilitation is crucial in order to maximise recovery after ABI. It is one of the most cost-effective interventions available to the National Health Service and reduces acute hospital stay, provides functional independence and facilitates a return to work. However, there are large variations in provision and access to services and a lack of neurorehabilitation personnel. "The current services are probably not what we would set up now, but there's lots of work in progress" concluded Alan.

The updated Rehabilitation Prescription (RP) was discussed by Hannah Farrell, University Hospitals Birmingham NHS Foundation Trust. The RP documents comprehensively the rehabilitation needs of the individual with ABI and identifies how those needs should be addressed longer term. The RP should be given to the patient on discharge and a copy sent to their General Practitioner to facilitate ongoing rehabilitation. Hannah said "The RP is not just a tick box exercise to generate money. It should be used for every patient with rehabilitation needs and a copy sent to their GP; this is a major challenge going forwards".

Chris Bryant MP and Chair of the APPG on ABI focused on the ongoing lobbying campaign surrounding the issues and recommendations set out in its report. "I'm dedicated to this cause because ABI is a hidden epidemic. I've campaigned so hard because it impacts on so many government departments". Chris summarised the report which outlines the critical role of neurorehabilitation in the ABI care pathway, and the need for RPs for all brain injury survivors following discharge from acute care so they know what neurorehabilitation they need. The report reviews the implications for children and young people with ABI when most of their neurorehabilitation takes place in the education system. The high incidence of ABI amongst offenders is discussed, as is the impact of neurorehabilitation on behavioural change and reoffending. The current issues in sport-related concussion are outlined as well as the need for an improved welfare system that is easily accessible. The report summarises the key issues and makes a number of crucial recommendations. Chris said that the APPG is determined to unite government departments and drive change for brain injury survivors.

Brain injury can make offending behaviour more likely. Being an 'offending type' can make having a brain injury more likely, and a brain injury can make people far more prone to the effects of alcohol which also increases their probability to offend. The prevalence of ABI in the offender population is significantly higher than in the general population. There is clear evidence of the different causality of brain injury between men and women in prison, with the females being at greater risk of repeated brain injury from domestic abuse. Dr Ivan Pitman, Brain Injury Rehabilitation Trust (BIRT) discussed the findings from BIRT's Brain Injury Linkworker service in a women's prison which is based on a stepped care model and focuses on identifying brain injury and implementing interventions to support the offender.

With regard to children and young people with an ABI, Professor Nathan Hughes, University of Sheffield said "Recognising brain injury is key to being able to provide the right support in schools, to prevent disengagement, exclusion and possible offending behaviour". Nathan discussed the issues surrounding the recognition and response to ABI and the discriminatory criminal justice processes. He emphasised the need to change systems and processes to ensure these young people obtain the appropriate and timely support, and ultimately prevent their propensity to go on to offend.

"The cornerstone of disability law is that the employer has a duty to make reasonable adjustments for the employee" said Emma Satyamurti, Leigh Day looking at the challenges of returning to work following a brain injury. Emma reviewed examples of 'reasonable adjustment' including a change of tasks, location, working hours and different approaches to managing absence and performance behaviour.

Dawn Astle concluded the formal conference programme by telling the story of her father, Jeff Astle, the footballer nicknamed 'the King' by fans, who won five caps for England. Jeff was the first British professional footballer to die from chronic traumatic encephalopathy (CTE), aged just 59 years. The impact of sport-related concussion on late dementia, CTE and other chronic neurological conditions is uncertain and further research is needed. The Jeff Astle Foundation was established in 2015 to raise awareness of brain injury and to provide support to those affected.

Various awards were announced at the conference. The winners of the UKABIF Film Award 2018 were Kathryn Cann for the County Durham and Darlington NHS Foundation Trust, Lauren Nicholas for the Royal Hospital for Neuro-disability, Anne Johnston and Jeremiah Humphreys-Piercy. The UKABIF Stephen McAleese Award for Inspiration went to Verity Fisher at the National Star College in Cheltenham.

UKABIF thanked conference sponsors Cygnet Health Care, Elysium, Irwin Mitchell solicitors, Leigh Day and Sintons Law, the many companies that exhibited and the excellent poster presentations.

Neurosurgical Update

Conference details: 16th July 2018, Aberdeen, Scotland. ***Report by:*** Nikhil Agarwal, 3rd year Medical Student, University of Aberdeen & Convenor Pragnesh Bhatt, Consultant Neurosurgeon, Aberdeen Royal Infirmary. ***Conflict of interest statement:*** None declared.

On July 16th 2018, a neurosurgical update was organised in Aberdeen with a view to invite Scottish colleagues. This meeting was catered for the multidisciplinary team including neurosurgeons, electrophysiologists, anaesthetists, speech & language therapists, physicists and even a medical student (me!). More importantly, the event became truly special because of our keynote speaker Professor Atul Goel, a well renowned neurosurgeon from India.

Mr Mahmoud Kamel, Consultant Neurosurgeon at Aberdeen Royal Infirmary, opened the conference with a presentation titled "Endoscopic treatment of anterior skull base meningiomas. Is it worth the hassle?" In this he discussed the pros and cons of using an endoscopic approach vis-à-vis conventional transcranial microsurgical approach – specifically in cases of tuberculum sella meningiomas.

Our keynote speaker, Professor Atul Goel, addressed the "Planning of Complex Brain Tumours". In this he shared his experiences with giant pituitary tumours and the challenges they bring. He presented various interesting cases he had seen over the years and the approach he took to managing those. These were very challenging to surgically resect, due to their sheer size and the invasiveness – especially when invading the cavernous sinus. However, he emphasised the fact that these tumours are confined to their dural boundaries and therefore understanding the anatomy helps massively.

Following on from this, Professor Goel spoke about the functions and importance of the cavernous sinus. He has discovered key concepts about the cavernous sinus, such as its importance in temperature regulation and its vital role in vision.

After this, Mr. Adnan Shaikh shared surgical management of a young patient with a dominant hemisphere AVM undergoing excision under awake craniotomy by Mr Pragnesh Bhatt, Consultant Neurosurgeon (and Convenor for the meeting). Dr Alan Forster, Consultant Clinical Neurophysiologist, and Penny Gravill, Lead Speech & Language Therapist, spoke about their experiences in awake craniotomies. They presented their involvement in initiating this service in Aberdeen and illustrated what their involvement was in this particular case. A full pre-operative language assessment, testing auditory and reading comprehension, was conducted. This was conveyed to the rest of the team to help plan and assess suitability for the procedure. Intra-operatively brain mapping and speech arrest were performed to make the surgery safe. The conclusion from this was that every member of the team had a valuable role and what makes such an operation a success was their coming together as a TEAM (Together Everyone Achieves More).

Dr Kathleen Ferguson Consultant Neuro-anaesthetist & President-Elect for the Association of Anaesthetists of Great Britain and Ireland, facilitating Professor Atul Goel visiting neurosurgeon from Mumbai, India.

After a lunch kindly sponsored by Safe Orthopaedics, Mr Likhith Alakandy, a neurosurgeon at Institute of Neurosciences, Queen Elizabeth University Hospital, Glasgow, outlined the anatomical variations of the vertebral artery at the craniovertebral junction (CVJ). It is important to understand, especially when planning surgeries involving C1 and C2.

Prof Goel then spoke about the technique he invented for atlantoaxial fixation. He described how he used lateral mass screws on C1 and pedicle screws on C2 to achieve fixation, which addressed a key problem of instability of the joint that required stabilisation. He also noted that through his method, the anatomical alignment of C1 and C2 was not required and found they had achieved 100% fusion in patients. He also spoke about the possible injury to the vertebral artery due to its course and referred back to what Mr Alakandy said, that anatomical knowledge and understanding is vital here.

Mr James Walkden, Consultant Neurosurgeon at Aberdeen Royal Infirmary, spoke on behalf of the department about their experience using the O-Arm. This was the first hospital in Scotland to use the O-Arm. The O-Arm is 3D computer assisted navigation based on CT imaging. It allows for multiple images to be taken which can be used to generate a 3D model. He noted that this imaging allowed for better accuracy for insertion of implants at the cranio-cervical junction as well as upper thoracic spine where routine fluoroscopy has some limitations. It was also highlighted that O-Arm is especially useful for training.

After a short break, Dr Brian Morrisey, Radiology Registrar at Aberdeen Royal Infirmary, gave an illuminating talk titled "Diagnostic uncertainty in High Grade Glioma: our experience learning from tumour chameleons". He explained that brain tumours could mimic different diseases which are common. The tumour is said to be a chameleon since it can make itself look like a different pathology. He then presented a case series, in which 13 cases were identified via the MDT over the past two years. The most common tumour chameleons were ischaemic and haemorrhagic stroke, followed by encephalitis. Out of these, the initial presumed aetiology was an ischaemic infarct in five of the cases, while in another three it was a haemorrhage. Following histopathology it was found that seven of the 13 were GBMs. It was concluded that GBM misdiagnosis can occur and that encouragement of early repeat imaging may be able to catch these chameleons promptly.

To finish off the day, there was a presentation by Mr Aimun Jamjoom, an ST4 Neurosurgical Registrar, on behalf of the British Neurosurgical Trainee Research Collaborative (BNTRC). He spoke about a research collaborative which explored external ventricular drainage. They found that the median time to infection for plain catheters was 8 days. In silver impregnated catheters it was 7 days and in antibiotic impregnated ones it was 11 days. Mr Michael Poon, Registrar from Edinburgh also spoke on behalf of the BNTRC, presenting a study about Chronic Subdural Haematomas. He concluded that the preferred method of treatment was burr hole drainage with a postoperative closed drainage system.

To end, a group photograph was taken, and the attendees were able to mingle with each other discussing future projects and collaborations.

From left to right:
Dr James Loan, Mr Aimun Jamjoom, Mr Mohammed Suheel, Nikhil Agarwal, Mr Mahmoud Kamel, Mr Pragnesh Bhatt, Mr Likhith Alakandy, Professor Atul Goel, Mr Anthony Wiggins, Mr Mohit Arora, Mr James Walkden

Cutting Edge Science for Parkinson's Clinicians

Conference details: 4 July, 2018, Birmingham, UK. ***Report by:*** Conference organiser Sarah Mehta, Neurology Academy.
Conflict of interest statement: PD Academy supplied the report..

Cutting Edge Science for Parkinson's Clinicians was an educational meeting sponsored by Bial Pharma UK Ltd, and delivered in association with the Parkinson's Academy. This one-day meeting, chaired by Dr Peter Fletcher set out to review advances in the clinical understanding of Parkinson's, and discuss how to build on these insights in routine clinical practice. As Dr Fletcher noted "Science provides the building blocks, the art is applying the evidence to the patients sitting in front of us".

Professor Huw Morris began his presentation on genetic testing with its conclusion – that there is, indeed, an increasingly urgent need to rethink how genetic testing is used in Parkinson's. In a world that is rapidly moving into a new era of readily available genetic testing, clinicians need to be ready to understand the complexities of ethics and consent issues that such testing brings. Patients increasingly want to know if their Parkinson's has a family basis, and we can expect increasing numbers of genetic-based cases as the population ages. Services must also be ready with the necessary framework for genetic and family counselling, as a genetic diagnosis has profound implications for the whole family.

Moving onto imaging, Dr Donald Grosset called for clinicians to also rethink how they use imaging within their clinical practice. Like genetics, the imaging field has taken big steps forward in recent decades, and Parkinson's services must consider how best to make use of these important tools. For example, in patients with a prominent tremor, DaTscan imaging can help differentiate between Parkinson's and essential tremor. However, an abnormal scan will not clearly differentiate between Parkinson's and Parkinson's plus syndromes. It is also vital that clinicians understand there are always exceptions to every rule. For example, the current threshold for detection on DaTscan means that patients with very early Parkinson's may initially show a normal scan, that changes with disease progression.

Dr Daniel van Wamelen took the audience on a whirlwind tour of therapies for Parkinson's. Starting with the available therapies, he noted that the new NICE guidelines continue to recommend a choice of MAO-B inhibitors COMT-inhibitors, or dopamine agonists as adjunct therapy to levodopa. In terms of new COMT inhibitors, Dr van Wamelen described recent studies that show that the COMT-inhibitor opicapone given once daily reduces OFF time by about an hour versus placebo, increases ON time without troublesome dyskinesia, and is non-inferior to entacapone given with each levodopa dose. Moving to more advanced disease, Dr van Wamelen described how both levodopa and apomorphine are 'old' drugs currently undergoing reformulation for improved delivery and wider utility.

Professor Ray Chaudhuri argued that despite tremendous progress in our understanding of Parkinson's, many challenges remain. These largely relate to the changes in the modern definition of Parkinson's and how the condition is now regarded as having distinct syndromic presentations based on non-motor manifestations. Clinicians must be aware that 'one size does NOT fit all', and that consideration of the non-motor subtypes can guide decision making. For example, if a patient has cholinergic involvement, they should be counselled regarding cognitive decline, anticholinesterase inhibitors and gait training. Likewise, patients with presentations affecting sleep should consider avoiding agonists acting at D3 receptors (implicated in sudden onset sleep) and be given early advice on issues such as driving and working with machinery.

"Walking is part of being human" began Dr Emily Henderson who explained that although walking is often assumed to become an automatic movement, dual tasking experiments show that walking does require frontotemporal function. Both the nucleus basalis of Meynert and the pedunculopontine nucleus undergo degeneration in Parkinson's, with more severe loss associated with cognitive impairment. Once gait is threatened, the brain has to use greater attentional resource, but this is difficult in the presence of a cholinergic deficit and can lead to problems such as falls. This has led to the hypothesis that improving cognition may prevent falls in people with Parkinson's and Dr Henderson discussed the accumulating evidence for improved cognition as a therapeutic target for reduced falls.

Using case studies, Dr Ben Wright highlighted the often life-changing benefits that deep brain stimulation (DBS) can offer patients, but stressed that these benefits are only achieved in the 'right' patients. According to the updated NICE guidelines, DBS can be considered for people with advanced Parkinson's whose symptoms are not adequately controlled by best medical therapy. However, even after decades of use, there remains a need for a better understanding of who to refer, when to refer them, and what benefits may be achieved, as well as an appreciation of the potential risks.

Closing with the controversial topic of neuroregeneration, Professor Roger Barker noted that this field of research is once again attracting investment. Attention had moved away from this approach in the face of famously failed trials, but Professor Barker suggested that the growth factor and stem cell trials may have been conducted too early – even before trying to understand the mechanisms of success in smaller studies. For example, clinical trials of growth factors have used suboptimal methods to deliver the treatment to the target site of action. While in some patients the effects of stem cell therapies were life changing, the clinical response varied from patient to patient. The challenge, therefore, is not whether this approach works, because it does in some patients, but rather how we can replicate this more consistently.

APPG on ABI launches report on acquired brain injury and neurorehabilitation

"Acquired Brain Injury is an invisible epidemic, and we need to ensure that the neurorehabilitation services required following a brain injury are 'fit for purpose'," said Chris Bryant, MP and Chair of the All-Party Parliamentary Group on Acquired Brain Injury (APPG on ABI), speaking at the launch of a report 'Time for Change: Acquired Brain Injury and Neurorehabilitation'.

There are more than 1.3 million people living with the effects of brain injury at a cost to the UK economy of £15 billion per annum or 10% of the NHS budget. Many more individuals now survive with an ABI, and many require continued access to neurorehabilitation, one of the most cost-effective interventions available, but there are large variations in the provision and access to neurorehabilitation services across the UK.

The report outlines the need for Rehabilitation Prescriptions for all brain injury survivors following discharge so they know what neurorehabilitation they need.

Chris Bryant concluded: "ABI impacts on many government departments so a task force is required to address the issues and recommendations as a matter of urgency. The APPG on ABI intends to unite all the departments involved in order to drive change for ABI survivors".

www.ukabif.org.uk/campaigns/appg-report

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"Severe migraine is a debilitating disease with limited treatment options. This approval marks another major milestone for galcanezumab, and offers the potential for reducing the number and severity of migraine attacks for patients and improving their quality of life." said Dr Arash Tahbaz, Senior Medical Director UK and Northern Europe.

The authorisation follows a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) that was received in September 2018. More details at https://bit.ly/2DLp1vn

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Healthcare professionals in the UK and Ireland can now sign up for access to The Academy of Medical Cannabis (www.taomc.org), Europe's first ever medical cannabis online education platform, where physicians can better understand cannabis-based medicinal products, giving them the confidence to consult on, and prescribe this new treatment option safely and effectively.

Professor Mike Barnes, Director of Education for The Academy of Medical Cannabis has developed a series of 'bite sized' modules providing guidance on this increasingly relevant treatment option.

The platform will also be made available to healthcare professionals in other European countries as their medical cannabis legislation is updated.

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Follow ebrain on Twitter (@ebrainnet) for updates on new learning sessions.

World Alzheimer Report 2018

The World Alzheimer Report 2018, *The state of the art of dementia research: New frontiers* brings together 21 of the global leading lights in dementia research. Written by journalist and broadcaster Christina Patterson (*Time Magazine, The Guardian, The Sunday Times*), the report tackles the complex questions surrounding dementia research. It looks at the hopes and frustrations and asks why there have been no major medical treatment breakthroughs for over 20 years.

The report looks at a broad cross section of research areas and with the continued absence of a disease modifying treatment, the report also features progress, innovation and developments in care research.

The report highlights an urgent need for increased and sustainable research funding. Through this report Alzheimer's Disease International is calling on governments to commit to a minimum of 1% of the societal cost of dementia to be dedicated to research. In 2018 the global societal cost is US$1 trillion.

A full list of interviewees can be found on page 46 of the report. See https://bit.ly/2PaSDZ0

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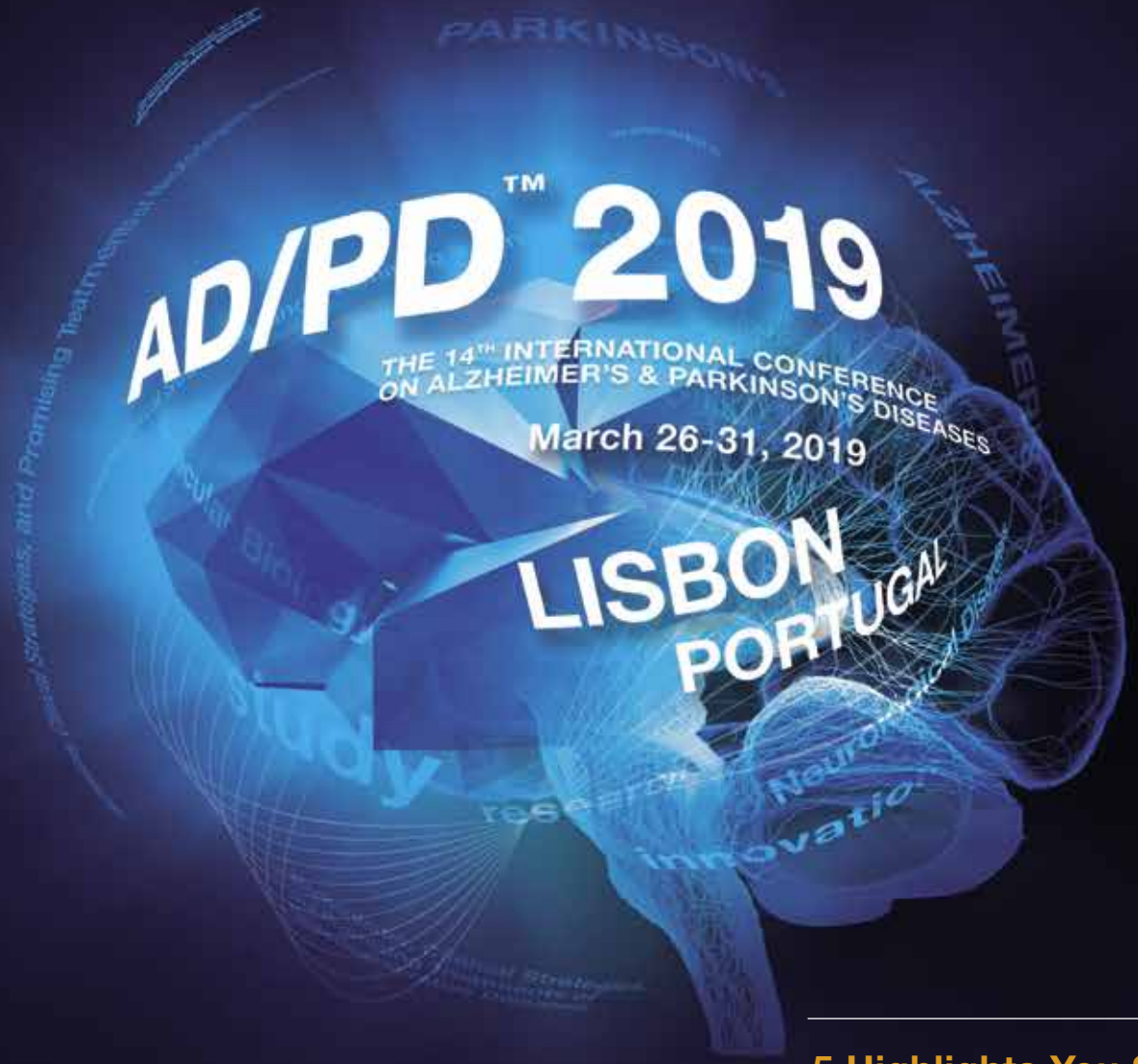

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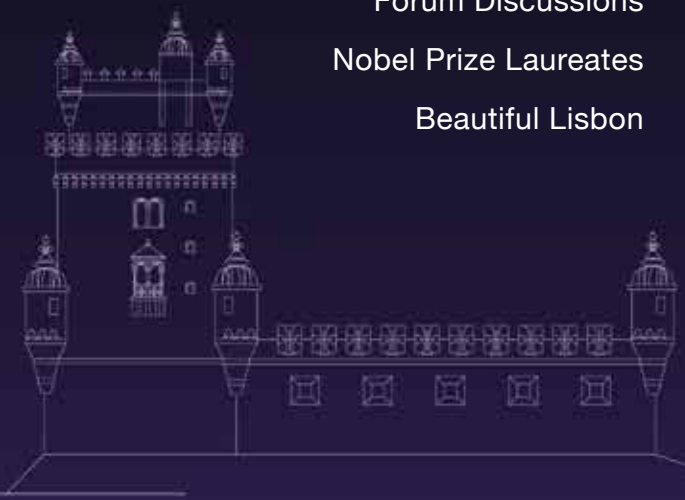

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See summary of product characteristics prior to prescribing for full list of adverse events

Presentation: 60 mg (yellow) / 30 mg (pink)/ 15mg (orange) edoxaban film coated tablets (as tosilate). **Indications:** Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA) and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **Posology and method of administration:** *NVAF* -The recommended dose is 60 mg edoxaban once daily with or without food. Therapy with edoxaban in NVAF patients should be continued long term. *VTE* - The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days with or without food. Duration of therapy (at least 3 months) should be based on risk profile of the patient. For NVAF and VTE the recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 mL/min), low body weight ≤ 60 kg and / or concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. The 15 mg dose of edoxaban is not indicated as monotherapy, and should only be used during a switch from edoxaban to VKA (see SmPC for full details). Edoxaban can be initiated or continued in patients who may require cardioversion. For transoesophageal echocardiogram guided cardioversion in patients not previously treated with anticoagulants, edoxaban should be started at least 2 hours before cardioversion to ensure adequate anticoagulation. Cardioversion should be performed no later than 12 hours after the dose of edoxaban on the day of the procedure. Confirmation should be sought prior to cardioversion that the patient has taken edoxaban as prescribed. If a dose of edoxaban is missed, the dose should be taken immediately and then continued once daily on the following day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal (GI) ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Uncontrolled severe hypertension. Concomitant treatment with any other anticoagulants e.g. UFH, low molecular weight heparins, heparin derivatives (fondaparinux, etc.), VKA or NOACs except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. Pregnancy and breast-feeding. **Special warnings and precautions for use:** Haemorrhagic risk: Use with caution in patients with increased risk of bleeding such as elderly on ASA and should be discontinued if severe haemorrhage occurs. The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for edoxaban is not available. Haemodialysis does not significantly clear edoxaban. Renal impairment: Renal function should be assessed prior to initiation of edoxaban and afterwards when clinically indicated. Not recommended in patients with end stage renal disease or on dialysis. Renal function and NVAF: A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful benefit risk evaluation. Hepatic impairment: Not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment. Edoxaban should be used with caution in patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN. *Surgery or other interventions*: discontinue edoxaban at least 24 hours before the procedure. If the procedure cannot be delayed, the increased risk of bleeding should be weighed against the urgency of the procedure. Edoxaban should be restarted as soon as haemostasis is achieved. *Prosthetic heart valves and moderate to severe mitral stenosis*: Not recommended *Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy*: Not recommended *Patients with active cancer*: Not recommended. **Drug interactions:** The *P-gp inhibitors* ciclosporin, dronedarone, erythromycin, or ketoconazole result in increased concentration of edoxaban and a dose reduction of 30mg is required. Edoxaban should be used with caution with concomitant *P-gp inducers* (e.g. phenytoin, carbamazepine, phenobarbitol or St John's Wort). Concomitant high dose ASA (325mg) or chronic NSAIDs is not recommended. **Undesirable effects:** Common: anaemia, dizziness, headache, epistaxis, abdominal pain, lower GI haemorrhage, upper GI haemorrhage, oral/pharyngeal haemorrhage, nausea, blood bilirubin increased, gamma GT increased, cutaneous soft tissue haemorrhage, rash, pruritus, macroscopic haematuria/urethral haemorrhage, vaginal haemorrhage, puncture site haemorrhage, liver function test abnormal. Uncommon: hypersensitivity, intracranial haemorrhage (ICH), intraocular haemorrhage, other haemorrhage, haemoptysis, surgical site haemorrhage. Rare: anaphylactic reaction, allergic oedema, subarachnoid haemorrhage, pericardial haemorrhage, retroperitoneal haemorrhage, intramuscular haemorrhage (no compartment syndrome), intra-articular haemorrhage, subdural haemorrhage, procedural haemorrhage. **Legal category: POM Package quantities and basic NHS costs: 60mg / 30mg – 28 tablets £49.00 15mg – 10 tablets £17.50 Marketing Authorisation (MA) number: EU/1/15/993/001-16 MA holder: Daiichi Sankyo Europe GmbH, Zielstattstrasse 48, 81379 Munich, Germany**

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Adverse events should be reported. Reporting forms and information can be found at yellowcard.mhra.gov.uk. Adverse events should also be reported to Daiichi Sankyo UK Medical Information on 0800 028 5122, medinfo@daiichi-sankyo.co.uk

References: 1. Giugliano RP *et al. N Eng J Med* 2013;369(22):2093–2104. **2.** LIXIANA® Summary of Product Characteristics. **3.** NICE Technology appraisal guidance [TA355]. September 2015. **4.** Scottish Medicines Consortium advice. SMC No. (1095/15). October 2015. **5.** Schulman S *et al. J Thromb Haemost* 2005;3(4):692–694.

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