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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

EPISTATUS®
Oromucosal Midazolam Solution (as maleate)

HELP IS BY THEIR SIDE

Epistatus® **(midazolam maleate)** is indicated for the treatment of prolonged, acute, convulsive seizures (PACS) in infants, toddlers, children and adolescents aged 3 months to less than 18 years.*

*For infants between 3-6 months of age, treatment with the standard dose of 2.5 mg (0.25 mL) should be in a hospital setting, where monitoring is possible and resuscitation equipment is available.

Epistatus® is now licensed in 4-age specific doses[1-4]:

Designed for Oromucosal Administration[1-4]

- Epistatus® is a **sweetened, sugar-free, slightly viscous** midazolam formulation[1-4]
- Epistatus® **2.5 mg** dose is contained in a volume of **0.25 mL, 5 mg** in **0.5 mL, 7.5 mg** in **0.75 mL**, and **10 mg** in **1 mL**[1-4]

Portable Design[1-4]

- The device is housed within a **tough** yet **lightweight** outer casing that is both **protective** and **tamper-evident**[1-4]

Prescribing Flexibility[5]

- **Single-unit pack** can be **tailored** to **PACS frequency** for individualised patient treatment[5]

Scan the QR code to visit www.epistatus.co.uk for further information about Epistatus®, including resources for clinicians and patients.

Prescribing Information

EPISTATUS® 2.5 mg, 5 mg, 7.5 mg, 10 mg oromucosal midazolam maleate solution. Please consult Summary of Product Characteristics (SmPC) before prescribing.

Presentation & composition: Oromucosal solution. Each pre-filled, oral syringe (1 ml) contains midazolam maleate corresponding to 2.5/ 5/ 7.5/ 10 mg midazolam. Excipients with a known effect: ethanol 49/ 99/ 148/ 197 mg/ml per dose, liquid maltitol 169/ 338/ 506/ 675 mg per dose.

Indication: 2.5 mg, 5 mg, 7.5 mg, 10 mg: Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children, and adolescents aged from 3 months to less than 18 years. Epistatus must only be used by parents/caregivers where the patient has been diagnosed to have epilepsy.

Dosage:

Age range	Dose	Labelled packaging colour
3 to 6 months, hospital setting	2.5 mg (0.25 ml)	Yellow
> 6 months to < 1 year	2.5 mg (0.25 ml)	Yellow
1 year to < 5 years	5 mg (0.5 ml)	Blue
5 years to <10 years	7.5 mg (0.75 ml)	Purple
10 years to < 18 years	10 mg (1 ml)	Orange

Carers should only administer a single dose. If the seizure does not stop shortly after administration, emergency medical assistance must be sought, considering prior instructions from the prescribing physician, or local guidelines. The empty syringe must be given to the healthcare professional. Patients should be kept under supervision by a carer who remains with the patient. A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice. Please see SmPC for full information on special populations.

Administration: For oromucosal use only. Using the prefilled oral syringe provided, administer, over a period of 2-3 seconds, approximately half of the prescribed dose to each buccal cavity. If difficult to get the syringe into the buccal cavity, administer the whole dose, over a period of 4-5 seconds, to one buccal cavity. For detailed instructions please refer to the SmPC.

Contraindications: Hypersensitivity to midazolam, benzodiazepines or to any of the excipients; myasthenia gravis; severe respiratory insufficiency; sleep apnoea syndrome; severe hepatic impairment.

Warnings & Precautions: For oromucosal use only. Take care to avoid the risk of choking. Use in paediatric patients aged 3 to 6 months should be limited to use only under supervision of health care professions where resuscitation equipment is available and where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available. Caution in patients with chronic respiratory insufficiency (may further depress respiration). Midazolam should be used with caution in patients with chronic renal failure or impaired hepatic function (may accumulate); or cardiac function (may decrease clearance). Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines. The concomitant use of Epistatus and opioids increases the risk of sedation, respiratory depression, coma, and death. Epistatus with opioids should be reserved for patients for whom alternative treatment options are not possible. The lowest dosage and shortest duration of concomitant use should be used. Inform patients and caregivers of the need to monitor closely for respiratory depression and sedation. Midazolam should be avoided in patients with a medical history of alcohol or drug abuse. May cause anterograde amnesia. Contains maltitol and ethanol.

Interactions: Please consult the SmPC for full details. Midazolam is metabolized by cytochrome P450 3A4 isozyme (CYP3A4). Inhibitors and inducers of CYP3A4 may increase and decrease the plasma concentration respectively. In the presence of CYP3A4 inhibition the duration of effect of a single dose of oromucosal midazolam may be prolonged; careful clinical monitoring is recommended. Midazolam may interact with other hepatically metabolized medicinal products. Co-administration with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression. Alcohol intake should be strongly avoided. The dosage and duration of concomitant opioid use should be limited.

Fertility, Pregnancy, and lactation: Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be considered in the event of administration in the third trimester. Midazolam passes in low quantities into breast milk (0.6%); it may not be necessary to stop breast-feeding following a single dose. Animal studies did not show an impairment of fertility.

Driving and machines: Midazolam has a major influence on the ability to drive or use machines. The patient should be warned not to drive or use machines until fully recovered.

Side effects: Respiratory depression occurs at a rate of up to 5%, although this is a known complication of convulsive seizures as well as being related to benzodiazepine use. Common: sedation, somnolence, depressed level of consciousness, respiratory depression, ataxia*, dizziness*, headache*, nausea, vomiting & fatigue*. Uncommon: hallucination*, agitation*, anterograde amnesia*, pruritus, rash, urticaria. Very rare: aggression*, movement disorders*, physical assault*, seizure, paradoxical reactions*, bradycardia*, cardiac arrest*, hypotension*, apnoea*, dyspnoea*. Increased risk of falls and fractures in the elderly and in those taking concomitant sedatives (e.g., alcohol). Angioedema may occur (frequency unknown). Consult the Summary of Product Characteristics for the full list of adverse drug reactions and before prescribing.

* These adverse reactions have been reported to occur when midazolam is injected in children and/or adults, which may be of relevance to oromucosal administration.

Legal classification: POM

NHS Price: 2.5 mg in 0.25 mL, 5 mg in 0.5 mL and 7.5 mg in 0.75 mL - £43.75, 10 mg in 1 mL prefilled syringe - £45.76

United Kingdom (Great Britain) Marketing Authorisation numbers: 2.5 mg PLGB 16786/0015, 5 mg PLGB 16786/0016, 7.5 mg PLGB 16786/0017, 10 mg PLGB 16786/0014.

Marketing Authorisation holder: Veriton Pharma Limited, Unit 16, Trade City, Avro Way, Brooklands Business Park, Weybridge, Surrey, KT13 0YF, United Kingdom.

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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Veriton Pharma Limited. Tel +44 (0) 1932 690325

1. Epistatus® 2.5 mg Oromucosal Solution Summary of Product Characteristics (SmPC). Veriton Pharma Ltd (2022). **2.** Epistatus® 5 mg Oromucosal Solution SmPC. Veriton Pharma Ltd (2022). **3.** Epistatus® 7.5 mg Oromucosal Solution SmPC. Veriton Pharma Ltd (2022). **4.** Epistatus® 10 mg Oromucosal Solution SmPC. Veriton Pharma Ltd (2022). **5.** Fisher, L. and Ludwig, C. (2020) 'Buccal Midazolam Solution for the Management of Prolonged Acute Convulsive Seizures: A Cost Analysis', *PharmacoEconomics – Open*, 4(1), pp. 171-179.

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COVER Self portrait by Yokabet Mekuria, shown at the Barbican's *differently various* exhibition which was curated by brain injury charity Headway East London (headwayeastlondon.org).

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Another issue of ACNR brings a range of diverting and informative articles to our readership.

Oliver Kleinig, Christopher Dillon Ovenden, Amal Abou-Hamden and Timothy Kleinig from Adelaide look at the latest evidence as to whether it is ever prudent to intervene neurosurgically when a patient has had an intracerebral haemorrhage. They explain why it is hard to run well conducted clinical trials to answer key questions in the field but foresee that minimally invasive surgical trials might be a way forward.

From Sydney, Rowena Mobbs 'tackles' clinicopathological controversies in chronic traumatic encephalopathy (CTE) and acknowledges an increasing understanding of the different types of head trauma that may lead to CTE, the difficulties of making a diagnosis in living patients and the need for disease specific biomarkers.

Abigail Clynch and colleagues from Liverpool appraise us of how molecular advances will improve and broaden the classification of meningiomas and how they might lead to novel treatment approaches.

Genny Hart, Rebecca Kimber, Emma Ladyman and Jane Richmond from London argue for the benefits of a multidisciplinary team approach to the management of progressive ataxias and provide insights into their experience managing these conditions at the National Hospital for Neurology and Neurosurgery.

AJ Larner's historical article is about how David Ferrier's public profile as a prominent neurologist led to his influence on three late 19th-century writers, Wilkie Collins, HG Wells and Bram Stoker.

John Cheyne's name lives on in the eponymous Cheyne-Stokes breathing which is readily recognisable to neurologists working in acute care settings. His career is the subject of JMS Pearce's biographical vignette.

We present a bumper crop of conference reports including Ismail Abdulfattah Ibrahim's report on the National Musculoskeletal and Pain Medicine Course and reports on the Dizziness and Balance Workshop by Maria Francisca Rocha, the UKABIF Annual Conference by Louise Blakeborough and the 9th Hull BASH National Meeting On Headache Disorders by Fayyaz Ahmed.

Our book reviews are from Rhys Davies reviewing "Neurology: A Clinical Handbook" by Charles Clarke and Timothy Boey who reviews "The Sleeping Beauties: And Other Stories of Mystery Illness" by Suzanne O' Sullivan.

We hope you enjoy this edition of ACNR.

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A list of our full editorial board can be found at www.acnr.co.uk/about-acnr/editorial-board/

An update on the Acute Surgical Management of Intracerebral Haemorrhage

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Abstract

Whether surgical intervention benefits patients or patient subgroups with intracerebral haemorrhage (ICH) remains controversial, despite numerous randomised controlled trials. However, ICH without intervention has an extremely high mortality rate, with significant disability in many survivors. Consequently, there are a wide variety of practices worldwide, from near-routine intervention in large ICH to near-complete avoidance of surgery. We review the evidence behind ICH surgical intervention, discuss peri-operative management, and also mention ongoing trials of early minimally-invasive surgery, which may strengthen the evidence base in this challenging field.

Intracerebral haemorrhage (ICH), despite being proportionally far less common than ischaemic stroke, causes a greater global burden of disease, due to mortality approaching 40%, and high disability rates in survivors [1]. Apart from stroke unit care, evidence for ICH surgical and medical interventions is weak, leading to large variations in clinical practice. This review covers current surgical controversies, techniques used for ICH, current guidelines for perioperative management, and outlines current trials aiming to strengthen the surgical intervention evidence base.

Surgical trial evidence overview

Surgical intervention for ICH is controversial. Excepting strong evidence of a mortality reduction for ventricular draining in patients with intraventricular haemorrhage (IVH) and hydrocephalus, there is no RCT-based Class 1 evidence for any surgical intervention, whether via minimally invasive surgery (MIS) or conventional craniotomy [2]. A key challenge faced in ICH Randomised Controlled Trial (RCT) design is navigating clinical equipoise in a highly fatal and comorbid condition. Investigators may deem enrolment unethical, or alternately, deem intervention a priori futile, limiting trial recruitment to narrow patient subpopulations. As clinical deterioration from mass effect is common, patient crossover to emergency surgical treatment may contaminate surgical trials.

The landmark (but neutral) craniotomy-based Surgical Trial in IntraCerebral Haemorrhage (STICH) found early surgery of patients with ICH (versus initial conservative treatment) was not associated with functional improvement. However, patients were only randomised if treating clinicians felt equipoise existed. Furthermore, screening logs were not kept and 25% of patients crossed over to surgical treatment, limiting interpretation [3]. Subsequent craniotomy trial individual patient meta-analysis suggested early (<8 hours) intervention may be beneficial [4]. Additionally there was potential benefit for patients aged<70, with moderate neurological deficits and ICH volumes, with superficial clots benefiting most [4]; however the STICH-2 trial which targeted some of these characteristics was neutral [5]. Despite a dearth of RCT-based evidence, surgical intervention for deteriorating patients with large cerebellar ICH is routinely performed on the basis of observational data strongly suggesting a mortality reduction; an RCT is unlikely.

Meta-analyses of MIS trials suggests overall benefit, although analysis is complicated by differing surgical techniques [6]. The largest MIS trial (MISTIE-III) did not demonstrate functional improvement benefit [7], however a mortality benefit was observed. Nevertheless, functional outcome seemed improved in patients with optimal evacuation (predefined as <15 mL residual volume) [7]. This suggested that surgical efficacy (influenced by technique and experience) may be a key determinant of functional outcome.

Surgical Techniques

Lacking clear evidence of optimal target population or technique, ICH surgical cohorts and approaches differ signifi-

cantly between regions and institutions. For instance, craniopuncture-based craniotomy is reported as 'standard of care' for ICH in China, but is largely not performed elsewhere [8].

The two main aims of surgery (which may overlap) are (1) to treat or prevent intracranial hypertension and (2) to limit perihaematomal brain injury.

(1) Preventing and treating intracranial hypertension

ICH can increase intracranial volume by multiple mechanisms (mass effect from the haematoma and perihaematomal oedema, hydrocephalus from IVH and/or secondary hydrocephalus from herniation). IVH-related hydrocephalus can be acute (from blood clot-related obstruction) or delayed (a post-IVH inflammatory response reducing cerebrospinal fluid resorption) [9]. Hydrocephalus may exist in isolation or complicate mass effect. While medical approaches to intracranial hypertension are largely ineffective [2], surgical intervention can ameliorate hydrocephalus and potentially prevent fatal transtentorial herniation by ICH debulking (reducing mass effect), and/or increasing intracranial volume (the latter is the focus of the SWITCH trial (Swiss Trial of Decompressive Craniectomy Versus Best Medical Treatment of Spontaneous Supratentorial Intracerebral Hemorrhage (www.clinicaltrials.gov NCT02258919)). It is probable (though it remains unproven) that surgical intervention can be life-saving. This is reflected in stroke guidelines internationally (for instance, the most recent American Heart Association guidelines state it might be considered in deteriorating patients as a lifesaving measure (Class 2B, Level of Evidence-C)). A combination of significant midline shift and deteriorating conscious state portends intervention, where deemed appropriate [10]. However, as summarised previously, it is uncertain whether and to what degree intervention may improve functional outcome beyond reducing mortality.

Ventricular drainage is strongly advised to reduce mortality in patients with hydrocephalus secondary to ICH +/- IVH contributing to impaired conscious state [2]. A recent meta-analysis suggests concurrent administration of intraventricular fibrinolysis may both decrease mortality and improve functional outcomes, especially when administered early [11], however in the CLEAR-III trial, a mortality benefit from fibrinolytic-enhanced ventricular drainage was accompanied by increased severe disability in survivors [12].

(2) Limiting perihaematomal injury

Excepting reduction of above mass effect benefits of haematoma evacuation are theoretical. It is possible, with ultra-early intervention, that haematoma expansion may be directly curtailed, however with most ICH expansion occurring in the first 2-3 hours [13], the optimal time-window for this benefit seems currently unfeasible. Haematoma evacuation may prevent ICH-related secondary injury. Intra-haematomal cytotoxic substances (most notably thrombin in the earlier time-frame and, later, iron from haemolysis) seem experimentally to mediate peri-haematomal injury and oedema [14]. Therefore their removal may be beneficial. Haematoma evacuation can occur via craniotomy or MIS, which is technically varied.

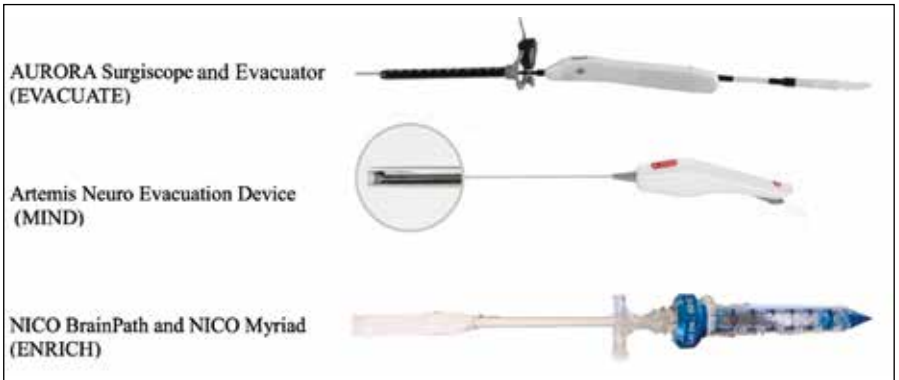

Figure 1: The devices used in current and upcoming minimally invasive surgical trials: The AURORA Surgiscope and Evacuator are being used in the EVACUATE trial. The Artemis Neuro Evacuation Device is being used in the MIND trial. The NICO BrainPath and Myriad are being used in the ENRICH trial.

MIS techniques

The three main approaches are craniopuncture, stereotactic thrombolysis and endoscopic removal. Craniopuncture is mostly utilised in China, and involves intra-haematomal placement of a YL-1 needle, skull fixation of the cannula and then haematoma aspiration, initially freely followed by fibrinolytic-augmented aspiration over several days. This approach is untested outside Chinese settings [8].

An analogous approach was tested in the Western MISTIE-III trial, enrolling patients with large (≥30mL) supratentorial ICH within 72 hours of onset, following a stability scan ≥6 hours after initial imaging. A 4.8mm cannula was inserted and 8-hourly fibrinolytic-augmented aspiration ensued (9 doses maximally) aiming for <15mL residual [15].

Direct MIS ICH removal can occur via several stereotactic endoscopic or endoscope-like approaches. Such techniques have included combining a Storz endoscope (Tuttlingen, Germany) via a 6.3mm introducer sheath with the Artemis evacuation system (Penumbra, CA, USA); combining the Aurora Surgiscope and Evacuator (Integra Lifesciences, NJ, USA. 11.5mm external diameter); and combining the BrainPath Endoport with the Myriad handpiece (Nico Corp, IN, USA, 15.8 mm external diameter) (Figure 1). These techniques allow direct visually-guided haematoma evacuation and facilitate direct surgical haemostasis, thus minimising rebleeding risk. The best balance of surgical visibility (via a large port) versus minimising invasiveness (via a smaller port) remains unclear.

Peri-operative management

Regardless of approach, recommended perioperative care of patients includes facilitation of haemostasis, management of blood pressure, glucose, and temperature and thromboprophylaxis, although direct evidence of benefit in surgical cohorts is scant [2].

Pre-operatively, effective anticoagulation reversal is required, with prothrombin complex concentrate, idarucizumab, or andexanet alpha as appropriate [2]. Platelet transfusion in patients on aspirin undergoing craniotomy may lower the risk of rebleeding and improve functional outcome (in contrast with non-surgical patients, whom it may harm) [16]. Desmopressin and tranexamic acid remain investigational [2]. Systolic blood pressure targeting 140 mmHg, but not substantially below, is non-harmful and potentially beneficial. Euglycaemia and avoidance of fever is recommended [2].

Thromboprophylaxis is highly recommended, initially with intermittent pneumatic compression and then potentially low-dose unfractionated or low-molecular-weight heparin [2]. Although prophylactic antiepileptic medications are not indicated, patients with active clinical or electrographic seizures should be treated [2]. Following surgery, once safe to transfer patients, care within a stroke unit will probably improve outcomes [17].

Current RCTs and Future Directions

Given treatment-related uncertainties and clinically unmet need, there is significant global interest in further ICH surgical trials, especially MIS studies. For robust and generalisable trial results, consecutive recruitment avoiding

'standard of care evacuation' is optimal (and, we feel, justified given the uncertainty of evidence reflected in guidelines.)

The ENRICH trial (Early MiNimally-invasive Removal of IntraCerebral Hemorrhage (www.clinicaltrials.gov, unique identifier NCT02880878)) has been presented (American Association of Neurological Surgeons and European Stroke Organisation Conferences, 2023) but not yet published. A functional outcome benefit was demonstrated from relatively early (<24 hrs) clot evacuation via the Brainpath Endoport compared with medical management in 300 participants. Benefit appeared restricted to lobar ICH patients, with an anterior basal ganglia treatment subgroup terminated early for futility. The MIND study (Minimally Invasive Neuro Evacuation Device (NCT03342664)) enrols 500 patients within 72 hours of ICH onset, randomised 2:1 to minimally invasive endoscopic evacuation with the Artemis System or to medical management.

These minimally invasive techniques are combined with ultra-early time-frame intervention in several studies underway or in late-stage planning, utilising ischaemic stroke triage and evaluation pathways, and leveraging the theoretical benefits from earlier evacuation, suggested by pre-clinical studies, observational data and surgical trial meta-analysis. The EVACUATE trial (Ultra-Early, Minimally inVAsive intraCerebral Haemorrhage evacUATion Versus Standard treatment (NCT04434807)), employs the Aurora Surgiscope and Evacuator (Integra Lifesciences, NJ, USA), randomising 240-434 patients with ICH volumes ≥ 20mL to ultra-early surgery (<8 hrs) or standard care (expected reporting December 2026). The DIST trial (Dutch Intracerebral Hemorrhage Surgery Trial) enrols 600 patients with ICH volumes ≥ 10mL, randomising to similarly early surgery with any CE-approved device (currently only the Artemis system) or standard care.

Together with other ICH trials in advanced stages of planning, these results will inform the next generation of surgical ICH care and potentially (individually or combined) demonstrate patient subgroups who benefit from particular surgical interventions.

Conclusion

Surgical best-practice care for ICH patients remains controversial. Currently the best evidence for intervention is in patients with hydrocephalus, cerebellar ICH and patients with impending transtentorial herniation who may accept survival with a severe neurological deficit. Ongoing surgical treatment trials will help determine definitively whether surgical ICH evacuation (especially using minimally invasive techniques) improves functional outcomes, and which patients may maximally benefit.

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BSPRM Annual Scientific Conference 2023

Winners of Best Published Paper at the BSPRM Annual Scientific Conference

Best Published Paper

The winning paper was "TEleRehabilitation Nepal (TERN) for People with Spinal Cord Injury and Acquired Brain Injury: A Feasibility Study," by Ram Hariharan, Stephen Halpin, Manoj Sivan, Raju Dhakal, Mandira Baniya, Rosie Solomon, Chanda Rana, Prajwal Ghimire, Sophie Makower, Wei Meng, Sheng Quan Xie, Rory J O'Connor and Matthew Allsop.

Read the full paper at bit.ly/3KnjLP3

Best Oral Presentation

Dr Harry Mee, Rehabilitation Medicine Registrar and Clinical Researcher, Cambridge, was awarded 1st prize for his oral presentation on "Randomised Evaluation of Early v Late Cranioplasty: A Pilot Study".

Read more at bit.ly/3rQt0B0.

Dr Harry Mee, winner of Best Oral Presentation

UCL Academics Elected to Academy of Medical Sciences

The Academy of Medical Sciences has elected 59 influential biomedical and health scientists to its respected Fellowship. The Academy is the independent, expert voice of biomedical and health research in the UK. Those newly elected include Professor Olga Ciccarell, Professor Henry Houlden and Professor Ley Sander.

Professor Ciccarelli's goal is to develop an AI-based model that predicts individual treatment responses in patients with multiple sclerosis. This crucial information will help patients to select the most appropriate treatment for them.

Professor Henry Houlden's clinical expertise is in inherited neurological disorders and movement disorders such as multiple system atrophy (MSA), ataxia, epilepsy, cognitive disorders and neuromuscular conditions.

Professor Sander has a specialist interest in epilepsy and its epidemiological aspects. He has a keen interest in global health and is involved in research programmes in China, Africa and Latin America.

The new Fellows have been elected to the Academy in recognition of their exceptional contributions to the advancement of biomedical and health science, cutting edge research discoveries, and translating developments into benefits for patients and wider society.

Professor Olga Cicarrelli

Professor Henry Houlden

Professor Ley Sander

Rimona Weil Receives the Wellcome Career Development Awards For Her Research Into Understanding Parkinson's Dementia

Rimona Weil

The focus of Rimona Weil's research 'Understanding why people with Parkinson's disease are at a higher risk of developing dementia' has been funded by the Discovery Research Career Development Award. Rimona's research makes use of advanced neuroimaging to understand what changes take place in the brains of people living with the condition.

As well as doing advanced imaging – using two different MRI scanners, Rimona's work uses PET imaging, measures of proteins in the plasma and cerebrospinal fluid and also MEG (magnetoencephalography, which measures or maps brain activity through magnetic fields generated in the brain). Together, these different modalities will provide information across a range of spatial scales. She hopes that in doing this with people living with the condition she can address the same question: how does dementia happen in Parkinson's?

For more information visit: https://wellcome.org/news/how-can-we-understand-parkinsons-dementia-better?

Innovation Award to Advance the Future of Science

Karger Publishers is seeking applicants for its fourth Vesalius Innovation Award. The award is aimed at early-stage startups in the Health Sciences and Publishing sectors that are developing innovative technological solutions with a significant impact in their respective fields. The winner will receive $15,000, while the two runners-up will be awarded $5,000 each.

The focus is on knowledge communication, patient centricity, and artificial intelligence. Early-stage startups in the health sciences are encouraged to submit their award applications via www.karger.com/via by September 3rd.

Chronic Traumatic Encephalopathy (CTE) - An Update and Overview

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Abstract
Chronic traumatic encephalopathy (CTE) is a neurodegenerative tauopathy associated with cumulative, prolonged exposure to symptomatic (concussive) or asymptomatic (subconcussive) repetitive head injuries (RHIs). An exposure-response effect has been demonstrated in American football along with case reports in high profile sports including Australian rules football, rugby union, rugby league, soccer, and ice hockey. Despite intense media interest in the professional contact and collision sports in which CTE has been demonstrated, CTE has been increasingly identified in a wide array of amateur sporting and also non-sporting environments including military related blast trauma, assault, and falls in this heterogeneous condition. Formerly thought a condition restricted to boxers in low case number, the clinical relevance of CTE neuropathological findings in footballers has become controversial in the new millennium, while nascent clinical and histopathological criteria are met by preliminary prospective biomarker studies. This article will explore aspects of clinicopathological controversies, the natural history of CTE, and frameworks for diagnosis and monitoring.

Shifting research scope

The field of CTE research has seen immense interest following the first report of CTE in American football by Omalu [1]. Prior to this, boxing was thought the main arena for developing CTE with an initial report by Martland in 1928 [2] on dementia pugilistica or punch-drunk syndrome before Critchley [3] coined the term CTE in 1957. Participants of contact collision sports [4–6], military service [7–9] or other trauma-related environments [10] are at risk of acquiring this neurodegenerative tauopathy caused by the cumulative neuropathological effect of repetitive head impacts (RHIs) [11–13]. A landmark study of 202 US football players found that 87% of the brains obtained were CTE positive [14]. The mean duration of play in mild and severe CTE pathology was 13 years (SD, 4.2 years) and 15.8 years (SD, 5.3 years) respectively. In 2013 a major push to understand the neuropathology of CTE was launched by the National Institutes of Health (NIH), supported by the Foundation for NIH's Sports Health Research Program with funding from the National Football League (NFL). The first NINDS/National Institute of Biomedical imaging and Engineering (NIBIB) consensus panel met in February 2015 [15] followed by the second consensus panel in 2021 [16] and following this the former categorisation of CTE into stages I-IV was superseded into two stages; 'low-CTE' where neuronal p-tau, in the form of neurofibrillary tangles, is restricted to one or more neocortical or subsulcal areas, and 'high CTE' where similar p-tau pathology is more widely distributed throughout the neocortex as well as other brain regions such the hippocampus, amygdala, thalamus, and cerebellar dentate nucleus, but the molecular mechanisms underlying this remain unclear.

Natural history of Chronic Traumatic Encephalopathy

Whilst single mild traumatic brain injury may be associated with prolonged impairment and disability, RHIs are associated with a cumulative worsening in cognitive, motor or behavioural outcomes [17,18]. The onset of an acquired neurodegenerative picture after RHIs across single or multiple domains is suggested by cognitive, psychological and behavioural decline over years in patients subsequently shown to have CTE [14,19,20]. Although the clinician may be confident that a patient presents with dementia, identifying the CTE subtype remains problematic in the absence of definitive biomarkers, and the correlation of in-life symptoms to the temporal onset of CTE neuropathology is still controversial [21–23]. Symptoms such as depression, anxiety and memory loss are often non-specific, subtle, may be treatment resistant, or are easily confounded by other factors. For these reasons, the term Traumatic Encephalopathy Syndrome (TES) is used to describe the in-life syndrome of CTE under revised NIH/National Institute of Neurological Disorders and Stroke (NINDS) research criteria [19]. For practical neurology purposes, the term CTE will also be used to describe the clinical manifestation in this article.

Progressive neuropsychiatric symptoms in CTE may associate with an increased suicide risk [24], although this remains controversial and unclear [25]. The Australian Sports Brain Bank (ASBB) has reported CTE in Australian rules football and rugby league with 12 of

21 former athletes who donated their brains for research being confirmed to have CTE. Of the 12 with CTE, 6 died by suicide [26]. Stern et al. (2013) described early data on survival, with mean symptom onset at 57.7 years (SD 5 18.3; range 25–82), mean dementia diagnosis 72.6 years (SD 5 8.5, range 56–83), and mean duration from diagnosis to death 8.0 years (SD 5 5.5, range 1–15) [27]. This would indicate a natural history of longer duration in CTE than many subtypes of dementia, with one large systematic review and meta analysis finding a mean survival from diagnosis in Alzheimer's disease (AD) of only 5.8 years (SD 2.0) versus non-AD survival from diagnosis (MD –1·12 years, 95% CI –1·52 to –0·72)[28]. In such an insidious disorder of younger people where dementia may not be suspected, it is possible that CTE has until now "flown under the radar" of standard practice. Interpreting the natural history of a patient presenting with possible CTE may assist in timely diagnosis, remembering the characteristic younger onset explosive neuropsychiatric and delayed cognitive features on a background of prolonged impairment.

No study has confirmed the prevalence of CTE in the general population, but a dose exposure-effect is described [20, 21] . Although all-cause mortality was lessened, theoretically due to a cardiovascular benefit with sport, higher rates of dementia mortality in soccer and dementia, Parkinson's disease and motor neuron disease in rugby union have been shown from epidemiological studies [29–31]. Early work suggests that CTE in professional sports is just the "tip-of-the-iceberg" in these popular pursuits, with one study finding that 91% of college players and 21% of high school players had CTE [14], and another adjusting for selection bias suggesting that around 10% of professional American footballers may suffer CTE [32]. The risk of CTE may increase according to earlier age of exposure as well as total duration of exposure in the order of a trebling for every 3 years of play and earlier manifestation of cognitive and neuropsychiatric features with play before age 12 [20]. A causal relationship between RHIs and CTE using the Bradford-Hill criteria has been newly established [11].

Patients with CTE are likely to face decades of future potential increased health burden marked by psychiatric and neurological morbidity consistent with the literature, early mortality, and carer distress. In 36 individuals with CTE a bimodal age distribution of neuropsychiatric presentation was found in the younger group and cognitive presentation in the older group [27]. Symptoms such as emotional lability, poor impulse control, memory loss, headache, language deficits, visuospatial difficulties, executive dysfunction, and global cognitive decline are reported, and this neuropsychiatric flavour is supported in subsequent studies. Single mild traumatic brain injury is often undisclosed by individuals, yet when apparent it constitutes a high burden of acute care [33]. The potential health burden of CTE from other causes such as intimate partner violence is coming into sharper focus [10].

Table 1. Preliminary Diagnostic Criteria for TES (Adapted from NINDS/NIBIB 2021)

	Clinical considerations
A. Substantial exposure to repetitive head impacts	• Age of first exposure concussion/subconcussion • Total exposure (years) • Multiple sporting and non-sporting exposure
B. Cognitive impairment	• Clinician report • Neuropsychological profile
C. Neurobehavioural dysregulation	• Change from baseline ○ Explosivity ○ Impulsivity ○ Emotional lability
D. Progressive course	• Informant • Clinical monitoring • Neuropsychological monitoring
E. Not fully account for by other disorders	• Exclude disorders ○ Neoplastic ○ Neuroinflammatory ○ Sleep ○ Headache ○ Psychiatric ○ Substance use ○ Genetic ○ Other neurodegenerative
F. Functional decline	• Impairment ○ Limitation ○ Mild dementia ○ Moderate dementia ○ Severe dementia
G. Supportive features	• Delayed onset • Motor involvement ○ Parkinsonism ○ Amyotrophic lateral sclerosis ○ Other • Psychiatric ○ Anxiety ○ Paranoia ○ Depression ○ Apathy ○ Other
H. Classify a. Suggested CTE b. Possible CTE c. Probable CTE d. Definite CTE with TES	• TES criteria ○ Core criteria met ○ At least 2 supportive OR ○ At least 3 supportive OR ○ Postmortem confirmation

Taking the Trauma History

Due to increasing public awareness, use of the term CTE has become mainstream by patients and practitioners alike, and may be a more practical term for in-life symptoms than TES. A categorical approach to the history and examination with objective decline are needed to confirm features of CTE, which may evolve in those as young as 25 [34]. It is important to ask the age of onset of exposure and age of retirement, any missed seasons from sport, and any head injuries outside of sport. It can be helpful to provide a medical definition of concussion that includes common signs and symptoms beyond the commonly held belief that concussion is solely a 'knock-out' or loss of consciousness. Ataxia and bradykinesia, convulsion, confusion and poor responsivity can be helpful immediate signs and the opportunity to educate patients and their families around these terms is often beneficial for future concussions.

Discussion may also centre around postconcussion syndrome, acute post-traumatic headache, delayed-onset persistent headache attributable to mild traumatic brain injury (International Classification of Headache Disorders ICD-3) and post-traumatic stress disorder due to assault or misadventure. Overlap with chronic migraine in patients with CTE can yield an opportunity for therapeutic intervention. Around one third of CTE patients will present with depression, and patients may either have symptoms at the time of retirement from contact or collision sport or in a delayed fashion [6]. Obstructive sleep apnoea, depression, attention deficit disorder, or other causes of cognitive impairment should be targeted for management, preferably before neuropsychological baseline.

The importance of repeated evaluation and a multidisciplinary approach similar to other dementia management, encompassing a neuropsychological baseline to inform individualised strategies for the management of these complex patients, cannot be overstated. Contextualising CTE within a spectrum of illness seen after RHIs and reinforcing that not

everyone exposed to RHIs will develop CTE can alleviate anxiety, especially in those of lower risk. Obtaining the collateral history to detect cognitive and neuropsychiatric manifestations is needed as patients are often impaired for insight, and neurological monitoring 1-2 yearly in those with suspected CTE is recommended. CTE follows affective, temporal, frontal, and global constructs familiar to the clinician encountering other neurodegenerative illnesses in the memory clinic, but a prominence of explosivity to minimal psychosocial triggers is seen, in the absence of evidence for other disorders. In our practice, we actively enquire about road-rage, queue-rage, verbal or physical explosivity, irritability and intolerance. Consideration of the safety of children within the family unit of a patient with suspected CTE and explosivity should be a priority. Mood stabilisation with agents such as lamotrigine or sodium valproate and low-dose antipsychotic therapy can routinely be considered as with other disorders of emotional lability, and cholinesterase inhibitors in those with suspected AD overlap.

Frontotemporal dementia, dementia with Lewy bodies and Parkinson's plus disorders should be considered within the differential. Magnetic Resonance Imaging and fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) scanning of the brain can be used to delineate subtypes other than CTE, for which there is no definitive test in life. Lumbar puncture for the exclusion of autoimmune encephalitis, Creutzfeldt-Jakob Disease, AD, infective, inflammatory or neoplastic aetiologies should be considered in addition to electroencephalogram (EEG) or other secondary testing.

Proposed screening, diagnostic and monitoring guidelines

Although concussion is often highlighted as a priority area for sporting protocol adaptation, accumulated RHIs and subconcussion remain the target for reducing the risk of CTE, recognising that concussion history is confounded by recall bias, poor detection, motivation to stay and play, and misinterpretation of what concussion constitutes. Evidence based recommendations (EBRs) and high quality clinical guidelines for CTE are not yet developed, requiring multicentre collaborative research to determine useful biomarkers for studying CTE in life. However, consensus based recommendations and practice points enable a useful interim step to improving outcomes in CTE.

Given the weight of evidence for CTE as a disease entity and need for a precautionary approach there should be no delay in taking steps towards preventative action. First age of commencement of contact should be reviewed by all risky sports, including cycling, extreme sports, equestrian and others beyond football, balanced by the need to obtain safety skills for tackling or falling appropriately best learned during motor development. The cardiovascular and social benefits of sport can remain during this transitional phase, training risk can be reduced, and protocols modified such as those by the Football Association in the UK (no heading under 12) or the pioneering Tackle Can Wait programme in the US. These approaches are built upon the recognition that the developing brain is vulnerable, and that exposure prior to age 12 appears to predict an earlier cognitive ($p<0.0001$) and behavioural/mood ($p<0.0001$) symptom onset by 13.39 and 13.28 years, respectively [5].

A new dilemma arises regarding the screening of individuals already at risk of CTE. The global population facing dementia is expected to reach 130 million by 2050. It is currently not recommended to screen the general population for dementia [35], however there is precedent interest in the benefit of early detection and risk modification in subpopulations, such as those with vascular risk [36]. The NIH/NINDS identify five or more years of organised environmental exposure in American football, including two years at high school level or above, as primary diagnostic criteria for TES. In current neurological practice, the monitoring of existing players that befit criteria for CTE could reasonably be performed five yearly, plus consideration of repeated neuroradiological and neuropsychological evaluation. Performing a baseline neurological assessment as athletes enter the elite or heavy contact environments might be integrated into industry, insurance, medical or governance frameworks.

Conclusion

Chronic traumatic encephalopathy should be considered in any patient with more than five years of repetitive mild traumatic brain injury exposure and a self- or informant-reported decline in daily functioning, behavioural dysregulation, and cognitive performance, guided by an increasing index of suspicion for those with a higher accumulated burden of RHIs. Neurological evaluation, neuropsychological testing and monitoring can assist in identifying the at-risk patient as well as individualised strategies for care and monitoring. Traumatic encephalopathy syndrome is both an old and new entity, from Harrison Martland's 1928 case reports to modern neuroscientific analysis. As with other neurodegenerative diseases, CTE can only definitively be confirmed neuropathologically, and finding sensitive and specific biomarkers presents an important and attainable goal for current research.

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Beyond the WHO classification of meningioma: using molecular diagnostics to guide management

Abstract

Meningioma are the most common primary brain tumour. Classically, meningioma are phenotypically grouped using the World Health Organisation (WHO) classification system. However, it is now understood that the WHO approach overfits tumours into three grades, resulting in similarly graded tumours displaying phenotypically distinct behaviour. There is a growing body of research investigating the molecular biology of these tumours, including genomic, transcriptomic, metabolomic, proteomic, and methylomic profiling. Such advancements in molecular profiling of meningioma are providing greater accuracy in prognostication of tumours.

Furthermore, a clearer understanding of tumour molecular biology highlights potential targets for pharmacotherapies. Currently, the routine application of in-depth tumour molecular analysis is limited, however as it becomes more widely available it will likely result in improved patient care. This review seeks to explore the important developments in meningioma molecular biology, discussed in the context of their clinical importance.

Introduction

Meningioma are the most common primary brain tumour, accounting for 38% of all Central Nervous System (CNS) neoplasms [1]. An association with increased age combined with a globally ageing population has resulted in an increased meningioma disease burden [2]. Other risk factors for meningioma development include ionising radiation, female sex and genetic disorders [2]. The management of symptomatic meningioma is surgical resection, with adjuvant fractionated radiotherapy and radiosurgery

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implemented in specific circumstances (e.g. sub-totally resected tumours) [2]. Following surgery, extent of tumour resection can be classified according to the Simpson grading system, or more broadly into gross- or sub-total resection. Key prognostic factors for recurrence include extent of resection, World Health Organisation (WHO) tumour grade, and use of adjuvant therapies [2].

The WHO CNS tumour classification system (Figure 1) received its most recent update in 2021 [3]. The 2016 version primarily used histopathological findings to classify meningioma into grades 1, 2, and 3 [4, 5]. Grade 1 tumours are the most common and least aggressive, whilst grades 2 and 3 are rarer, more aggressive, tumours [1,2]. Survival rates vary between grades, with grade 1 being the highest (10 year relative survival 96.8%), then grade 2 (90.2%), and grade 3 having the lowest survival rates (30.4%) [6]. Notably, the 2021 update deviates from the previous system by the including a number of molecular factors. The presence of TERT promoter region mutations and CDKN2A/B homozygous deletion are now diagnostic of grade 3 meningioma [3,7,8]. Furthermore, the presence of rhabdoid and papillary histological sub-types are no longer independently diagnostic for WHO grade 3 meningioma [3].

The changes in the 2021 WHO classification reflect a paradigm shift in the field of neuro-oncology. Advancements in the genomic, transcriptomic, methylomic, proteomic, and metabolomic profiling have resulted in higher fidelity characterisation of CNS tumours. Despite the inclusion of prominent molecular factors, the current WHO classification does not fully represent the vast heterogeneity represented by the variable clinical behaviour seen in meningioma [2]. Advanced molecular characterisation of tumours also widens the potential for novel treatments by targeting the essential drivers of neoplastic growth. There are currently a number of targeted therapies for meningioma under investigation [9,10]. As our understanding of tumour biology grows, monitoring and treatment may be tailored to specific genetic aberrations, allowing intensification for aggressive phenotypes and relative sparing of benign acting tumours. Despite demonstrating superiority over the WHO classification, very few centres offer fully integrated molecular diagnostic approaches as routine clinical practice. This review highlights the prominent meningioma molecular factors being investigated and discusses their importance, as neuro-oncology moves ever closer towards a fully personalised medicine approach.

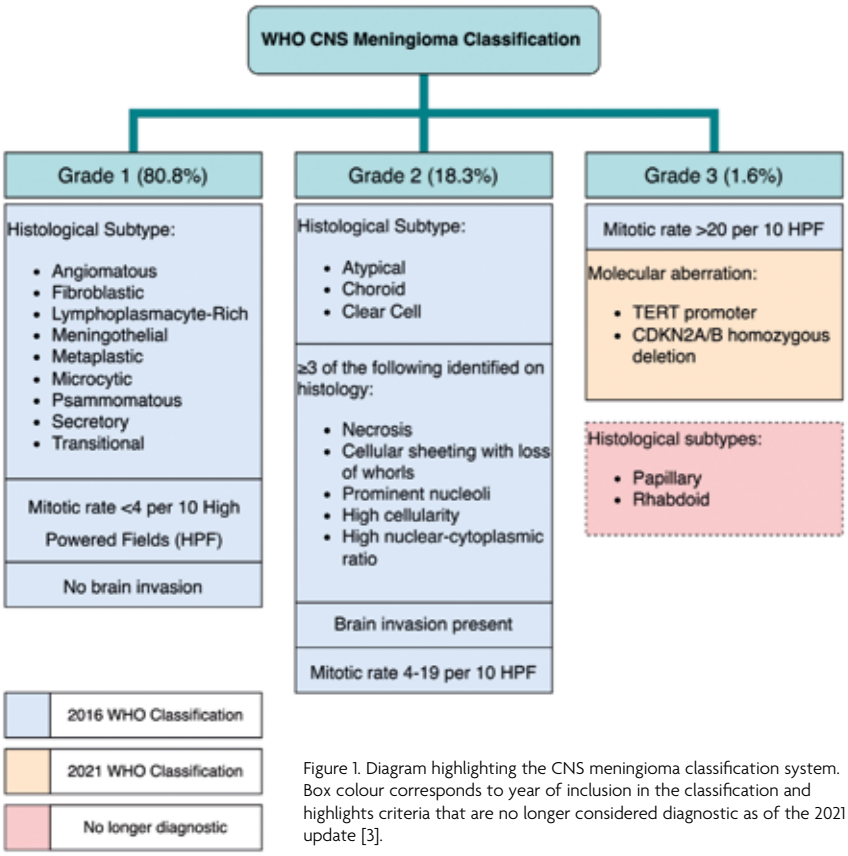

Figure 1. Diagram highlighting the CNS meningioma classification system. Box colour corresponds to year of inclusion in the classification and highlights criteria that are no longer considered diagnostic as of the 2021 update [3].

Neurofibromatosis 2

Loss of chromosome 22 was the first recurrent genetic alteration found in meningioma [11]. Further examination of this alteration found loss of heterozygosity on chromosome 22q (LOH22). Coding for Merlin, NF2 is considered the most probable meningioma-associated gene located in this region and is found in 50-60% of meningioma [11-14]. Merlin is thought to link the actin cytoskeleton to the plasma membrane and acts as a tumour suppressor [15]. The exact biochemical mechanism by which Merlin works is not fully understood [16].

NF2 can be involved in hereditary neurofibromatosis type 2. Meningioma in this circumstance are described as NF2 associated Meningioma. Similarly, individuals without the condition can develop sporadic meningioma that contain a NF2 mutation – this is described as NF2 mutated meningioma. A substantial alteration in Merlin is needed to result in meningioma development, with mutational frequency increasing with WHO grade [13,14]. No NF2 hotspots have been located at present [13]. NF2 frequency varies across histopathological subtypes, for example it is significantly lower in meningothelial meningioma [14]. It has been proposed that separation into NF2 and non-NF2 meningioma could be a reasonable adjustment to the WHO classification. However, tissue analysis for NF2 is not routine in clinical practice. NF2 mutations are not believed to contribute to malignant progression [14]. NF2 is not an independent risk factor for recurrence, therefore as a prognostic marker of malignancy and recurrence NF2 does not appear to be useful.

However, NF2 appears to be a useful focus for targeted therapies. When examining clinical implications of NF2, Brastianos et al have defined a NF2 specific treatment arm testing FAK inhibitors [17] in the ongoing Alliance A071401 clinical trial. FAK inhibitors for NF2 mutations demonstrate excellent tolerability and improved progression free survival (PFS) compared to controls that warrant further investigation in larger trials [17]. Brigatinib is a multiple tyrosine kinase inhibitor, which also affects FAK as one of its targets. Early research has demonstrated that it may be an effective treatment of NF2 deficient meningioma, however further investigation is required [16]. Merlin has a role in inhibition of mTOR tumour growth pathways. Inhibitors of mTOR such as vistusertib are currently under investigation and early results in aggressive subsets of meningioma show promise [18]. FAK and mTOR inhibitors are a promising advancement in targeted meningioma therapy, in individuals with NF2 associated or NF2 related meningioma.

Telomerase Reverse Transcriptase

Already incorporated into WHO classification of glioma, Telomerase Reverse Transcriptase (TERT) promoter mutations extend telomeres to produce immortal cancer cells [3, 7]. TERT mutations are found in a minority of tumours overall. Mutations in TERT are most common in high grade meningioma [19], which contain fewer targetable mutations when compared to low grade meningioma, however, such mutations are predicted to be neoantigens [20]. TERT mutations have been correlated to a high neoantigen load in all cancer types [21]. Similarly, TERT promotor mutations are associated with an increased risk of malignant histopathological progression [22].

> *There is a growing body of research investigating the molecular biology of these tumours, including genomic, transcriptomic, metabolomic, proteomic, and methylomic profiling. Such advancements in molecular profiling of meningioma are providing greater accuracy in prognostication of tumours.*

The presence of TERT promotor mutations is linked to poor prognosis, reduced time to progression and increased risk of malignant histopathological progression in meningioma [7, 22]. Identification of TERT promoter mutations would identify those patients at higher risk of recurrence following treatment and might prompt the use of more frequent MRI surveillance and clinical follow-up. The importance of TERT mutations as a prognostic factor is exemplified by its inclusion as a signifier of grade 3 tumours in the updated WHO classification system [3].

Clinically, TERT mutations raise a number of questions regarding treatment and alternative therapies. TERT mutations are associated with high risk of recurrence following radiotherapy, which brings into question the clinical utility of adjuvant radiotherapy in this patient cohort [25]. The development of an alternative targeted treatment would offer clinicians a solution to this dilemma but this is not yet available. High neoantigen load in high grade meningioma presents the opportunity for immunologic therapy targeting TERT associated neoantigens. Similarly, TERT promotor mutation associated with histopathological progression allows for prospective targeting of low-grade meningioma with this mutation using aggressive TERT immunologic therapy.

Other Molecular Mutations

Recent studies have identified phosphoinositide 3-kinase (PI3K), hereditary haemochromatosis (HH) and tumour necrosis factor receptor associated factor (TRAF7) mutations as significant markers of recurrence risk [23]. Kruppel like factor 4 (KLF4) mutations are protective against recurrence [23]. PI3K demonstrates the earliest recurrence rate, and along with HH is correlated to multiple driver genes [23]. Definitive identification of optimal driver genes in these mutations would allow for prognostic stratification and classification of affected meningioma, e.g., PI3KH1047R and SMOL412F respectively [23]. Similarly, it would allow for further development of targeted treatment clinical trials [17].

Alternative molecular markers to identify clinically aggressive meningioma are still relatively unexplored. Several studies have been performed but there can be a discrepancy in the presence of mutations between studies due to varying cohort sizes [37-39]. DNA Topoisomerase II Alpha (TOP2A) labelling is associated with a shorter overall and progression free survival, whilst N-MYC downstream-regulated gene 2 (NDRG2) is established as a marker of tumour aggression [24,25]. Polycomb Repressive Complex 2 (PCR2) activity is increased in more aggressive meningioma [24]. Larger scale studies are needed to validate these biomarkers before they can be considered clinically useful and incorporated into the WHO classification.

Transcriptomics

Patel et al performed primary transcriptome analysis of meningioma samples [26]. They found meningioma samples clustered into three clinically significant groups: Type A, B and C [26]. These clusters demonstrated significant differences in mitotic activity (MIB1)- highest in Type C [26]. Transcriptomal changes in the form of DREAM complex loss correlate with the higher MIB1 in Type C meningioma [26]. DREAM complex bound with RB-like proteins allows a cell to remain quiescent [26]. However, when associated with MYBL2 and FOXM1 the DREAM complex becomes activated and subsequently drives cell proliferation [26]. Elevated FOXM1 and MYBL2 is associated with more aggressive meningioma [26-28]. Identifying loss of repressive DREAM complex as a characteristic feature of high-grade meningioma, would allow clinicians to identify individuals most at risk of recurrence and tumour aggression. This information would guide follow up and treatment decisions.

Meningioma sample clustering was not associated with WHO classification as per the 2016 classification. Transcriptomic clustering samples displayed a longer PFS despite being classified as WHO grade 2 meningioma. Recurrent tumour samples were found to be of the same transcriptomic clustering of the original tumour. Identifying similarities between original tumour and recurrent tumour offers scientists an insight into the pathophysiology of meningioma recurrence. Similarly, identifying a common transcriptomic change across meningioma allows for treatments to be developed that could prevent or rapidly treat tumour recurrence (e.g. restricting MYBL2 or FOXM1 expression).

Metabolomics

Metabolomics refers to the study of the metabolome – the biochemical profile of a cell or organism. Metabolomic research has been used in a range of different cancer types to identify diagnostic biomarkers, driver mutations and monitor disease progression.

A metabolomic study by Masalha W et al identified two clusters of meningioma samples marked by metabolite alterations that separated samples by WHO grades, proliferation and PFS [29]. Another study demonstrated that meningioma metabolome provides a way of identifying aggressive meningioma allowing for personalised treatment [30]. Identification of metabolites within tumour samples that could identify more aggressive meningioma and those more at risk of progression could allow clinicians to approach such tumours with a more aggressive surgical approach and follow patients more closely than those without.

Away from meningioma research, in pheochromocytoma, paraganglioma and breast cancer metabolomics have been used to detect driver mutations with indicative metabolite profiles [31]. The ability to detect optimal driver mutations within meningioma would allow for the development of targeted therapies and aid prognostic stratification [23].

Methylome Profiling

The process of methylation has a number of important functions in both physiology and pathophysiology. It helps prevent expression of harmful intergenetic regions of DNA, plays an important role in regulating gene expression through variable methylation of CpG sites, and functional knockout studies in methylation regulating proteins have demonstrated its importance in normal CNS development [32]. Abnormal activity of methylation regulating proteins, such as DNA methyltransferases (DMNT), are implicated in meningioma pathogenesis [32]. Aberrant methylation results in gene silencing by blocking the transcription of genetic material [33]. Pro-oncogenic changes in DNA methylation occur in the initial stages of tumour formation, meaning it is an early indication of the disease process [33].

Early research into the role of methylation as a prognostic classifier for meningioma did not provide a significant improvement over the WHO classification [34]. However, it did demonstrate the feasibility of using methylation to classify tumours, thereby laying the groundwork for future studies. In 2017, Sahm et al published a methylation based classification and grading system of meningioma, based on multi-institutional data [35]. There are a number of key findings to highlight from this study. Firstly, using genome wide methylation signatures, meningioma were successfully distinguished from other primary brain tumours [35]. Next, application of hierarchal clustering broadly identified two cohorts of meningioma based on their methylation expression. Within these cohorts, a further six subgroups were identified and designated Methylation Classes (MC) ben-1, MC ben-2, MC ben-3, MC int-A, MC int-B, and MC

mal [35]. Kaplan Meier analysis demonstrated a reduction in PFS from the benign (MC ben-1, ben-2, ben-3), to intermediate (MC int-A, int-B), and the malignant (MC mal) groups. Crucially, both the crude molecular classification and a combined version were shown to outperform the WHO classification system in predicting PFS [35]. This improvement reflects the ability of methylation to better distinguish genetically unstable 'low grade' and stable 'high grade' meningioma [2].

Currently, methylation analysis is not a widespread component of pathological meningioma tissue analysis, owing to limited access to facilities and the associated cost. However, as the technology improves, becoming cheaper and more widely available, analysis of meningioma methylation will provide a greater degree of accuracy when clinically stratifying risk of recurrence. Subsequently, patients may be better selected for adjuvant therapies and intensities of follow-up, leading to an improvement in disease management and patient experience. Methylomics have also been used to identify potential new treatments for meningioma. A gene enrichment study using methylation profiling demonstrated that patterns associated with tumour recurrence may be sensitive to Docetaxel, a chemotherapy agent already used in the treatment of other cancers [36]. Methylome profiling may prove useful in identifying systemic therapies for aggressive subsets of meningioma, beyond simply targeting specific driver mutations. Finally, multifaceted integrative molecular classification systems are superior to uni-dimensional pathological analysis, and methylome profiling forms a key component of these updated approaches [37].

Feasibility

Despite the promising discoveries in meningioma classification there are still a number of challenges to integrating molecular diagnostics into the current WHO classification. The majority of which studies looked at molecular diagnostics have been performed on tumour samples from a retrospective cohort. This data needs prospective validation in order to confirm retrospective results. Similarly without effective pharmacotherapy (e.g. TERT targeted therapies), clinicians must balance the benefits of identifying relevant mutations with the risk of delayed patient time to diagnosis. Finally, in patients who are already diagnosed, it is necessary to rerun tests and gain more information on their tumour without being clear on the benefit this would have for the patient.

Away from the biological issues there are a number of practical issues that must be considered when assessing the feasibility of an integrated molecular classification. Hospital infrastructures may not have the capacity or technology to perform complex additional tests on patient samples, meaning testing must be outsourced. Outsourcing to commercial companies not only incurs a large cost but prolongs the time for results to be returned to treating clinicians. Simultaneously, outsourcing to companies with varying capacities could result in some results returning prior to others as demonstrated in other brain tumours (e.g. awaiting MGMT methylation status in glioma samples). Subsequently, patients have a delayed time to final diagnosis, longer waiting time and potentially raised anxiety. Clinicians have to deal with having a fragmented pathological report, and make difficult decisions around formal diagnosis and when to invite patients to clinic. To develop an integrated molecular classification system, multiple analysis techniques are required, including whole-exome sequencing, copy number, DNA methylation, and mRNA sequencing [37]. Researchers have attempted to correlate complex integrated molecular classification groups to more clinically practical methods, such as protein expression on immunohistochemistry [37]. However, further evidence is needed to justify the validity of these findings.

Conclusions

Neuro-Oncology is currently in the process of a molecular renaissance. Translational research is providing new insights into how clinicians can more accurately group phenotypically alike meningioma. This review has highlighted some of the key molecular factors of interest. Genomic, transcriptomic, metabolomic, and methylomic analysis is able to provide more representative prognostication of tumours, compared to the conventional WHO classification. Although the newly updated WHO classification reflects the importance of appreciating molecular factors, it still produces overly homogenised groups of behaviourally dissimilar tumours. Integrated molecular classifications provide even greater degrees of prognostic ability, at the expense of further reduced clinical applicability. Uncovering meningioma molecular biology is also providing powerful insights into potential targeted therapies, which may further improve patient care should they prove successful.

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Preview: Brain/Mind Interface, Clinical & Medicolegal Challenges

Join us for a thought-provoking conference on Oct 05, 2023, at The Royal College of Physicians, 11 Saint Andrews Place, London, NW1 4LE. This in-person event will explore the challenges and opportunities associated with the brain/mind interface.

Whilst cultural, psychological and social factors impact the access to interventions such as vaccination, inequalities of access to assessment and treatment for complex neuropsychiatric problems are also driven by similar factors but are magnified by socio-cultural perspectives of what 'illness' is, what constitutes a disability, the differences between visible and invisible impairments and the impact of stigma on acceptance of both people with these conditions and the healthcare professionals who treat them.

The challenges of a lack of parity of esteem for physical, cognitive, and mental illness are played out day to day across a wide number of settings not only in health and social care but also in medicolegal practice. This conference seeks to understand some of the problems that health inequalities cause and solutions for them.

Experts in the field will share their insights and experiences, and there will be ample opportunity for networking and discussion. Whether you are a clinician, researcher, or legal professional, this event is not to be missed.

Multidisciplinary Management of Progressive Ataxia

Genny Hart, BSc (Hons), MCSP, is a Highly Specialist Physiotherapist at The National Hospital for Neurology and Neurosurgery, UK. She has specialist knowledge of complex long term neurological and neurodegenerative conditions. She has a specialist interest in ataxia and is part of the outpatient ataxia MDT. Genny set up the virtual physiotherapy ataxia exercise and education group.

Rebecca Kimber, BSc (Speech Pathology), MRes Student, is a Highly Specialist Speech and Language Therapist at The National Hospital for Neurology and Neurosurgery, UK. She has specialist knowledge of complex neurological and neuromuscular conditions, functional neurological conditions, facial palsy, differential diagnosis and works as part of the inpatient and outpatient neurology team. She has a specialist interest in ataxia and is part of the outpatient ataxia MDT. Rebecca set up the virtual speech and language therapy ataxia communication and education group.

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Paola Giunti MD, PhD, studied medicine at La Sapienza University of Rome, Italy. She completed her training in neurology in the same university and obtained her PhD researching neurogenetic disorders and the dominant ataxias.

She is now Professorial Research Associate in the Department of Clinical Movement Neurosciences at UCL Queen Square Institute of Neurology and Honorary Consultant at the National Hospital for Neurology and Neurosurgery.

She established the first Ataxia Centre at the NHNN in 2005, a robust model of translational clinical service. This has been accredited as the first centre of clinical excellence in the UK by Ataxia UK and more recently by the National Ataxia Foundation, charities of ataxia patients in the UK and USA respectively. On this model, two other centres have been established in the UK. In this setting she has established the first Ataxia Multidisciplinary clinic that sees a Neurologist specialised in ataxia together with a speech and language, occupational and physio therapists.

Abstract

The National Hospital for Neurology and Neurosurgery (NHNN) hosts a specialist centre for people living with Progressive Ataxias. Patients attend from across the UK for differential diagnosis, specialist opinion, expert assessment and exploration of treatment options. This article discusses the treatment and management considerations of the multi-disciplinary team in the context of a condition with a huge variety of symptoms and limited evidence base for clinically effective treatment. It highlights the importance of tailored treatment focused on symptom management and optimising participation. It also discusses service initiatives that enabled patients continued access to treatment during the COVID-19 pandemic. These initiatives were proven to be very successful and therefore continue to run today.

Key Points

- The management of progressive ataxias requires an MDT approach to capture all facets of this complex disease.
- Best treatment approach requires that therapy is tailored to each individual's needs from each MDT member.
- Allied health professionals play a vital role in empowerment and education of people with progressive ataxias to effectively manage symptoms and optimise function.
- Group therapy is a novel approach to treating people with progressive ataxia that requires further research.

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Introduction

Progressive ataxias are rare and complex disorders affecting an estimated 10,000 adults in the UK [1]. Diagnosing progressive ataxia is challenging due to the high number of genetic causes and is often based on clinical presentation. The Global 100,000 Genome Study has isolated and identified the causal genes, identifying over 40 varieties of spinocerebellar ataxias [11]. This has improved the knowledge of how the differing types might progress. In some ataxias, the neuropathology is purely cerebellar, however, extrapyramidal, spinocerebellar tract, dorsal column, vestibular and peripheral nerve involvement can be present [12,5]. The main clinical features of progressive ataxias are gait and limb ataxia, imbalance, gaze-evoked nystagmus, intention tremor, dysphagia and dysarthria [3]. The progressive nature of ataxia often results in loss of function in daily activities, independence and quality of life [3,4]. Although there is better understanding of the progression of the symptoms of ataxia, there is little high-quality evidence-based-practice to guide intervention [13]. Most evidence is based on specific genetic phenotypes, highlighting the challenges of generalising treatments to all ataxias [14].

Treatment and Management

There are research trials investigating pharmacological and gene therapies for ataxia [7], however proven curative treatment or disease-modification is absent. Primary treatment of progressive ataxia is based on symptom management and maintenance of function. The large variation in symptom presentation makes the management of ataxia challenging. Consensus guidelines for the management and treatment of progressive ataxias was developed by an expert group of clinicians in 2016 [1,4].

At NHNN, patients with ataxias are examined in the MDT ataxia clinic comprising of a Consultant Neurologist expert in ataxia, Physiotherapist, Occupational Therapist (OT) and Speech

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> *Interventions by allied health professionals play a crucial role in the management of people with progressive ataxias due to the complexity and change in symptoms over time. Long-term collaboration, conveyance of hope and supporting day-to-day improves self-identity, self-esteem and sense of control of symptoms.*

and Language Therapist (SLT) to identify their specific and complex ataxia needs and to ensure that a holistic approach is taken. The specificity of this clinic means the history of the patient's progression, in keeping with the stage of their disease, is considered in the context of their treatment and intervention. For example, people who have a diagnosis of Friedrich's Ataxia commonly have reduced muscle mass due to peripheral neuropathy and therefore intervention for foot and hand function is vital. The aim of the clinic is to identify the person's main daily challenges, provide education and advice, discuss medical and pharmacological management and signposting to relevant local services.

Allied Health Intervention

Beyond diagnosis, understanding of management options amongst health care professionals is lacking, and as such, patients face enormous challenges in both understanding their illness and obtaining appropriate treatment. Interventions by allied health professionals play a crucial role in the management of people with progressive ataxias [4] due to the complexity and change in symptoms over time. Long-term collaboration, conveyance of hope and supporting day-to-day improves self-identity, self-esteem and sense of control of symptoms [12].

Interventions should be individually tailored to support: specific goals related to activity and participation; integration of restorative and compensatory strategies; targeted impairment based therapy to optimise and preserve function and prevent secondary complications [12]. People with ataxia have overlapping symptoms that affect their functioning. For example, they often experience fatigue which impacts on their balance and speech production. Working as an MDT to optimise symptoms and not in isolation is important for holistic care.

Physiotherapy

There is emerging evidence to support positive outcomes for patients with progressive ataxias through physiotherapy intervention [13] including: falls prevention; optimisation of mobility and function; improved quality of life (QOL); reversal of deconditioning [2].

An in-depth assessment covering balance, gait, coordination, core stability, strength, endurance, vestibular function, muscle length, spasticity and posture is required [16]. Interventions might include:

- Provision of individualised HEPs targeting ataxic impairments alongside cardiovascular fitness and global strength.
- Dynamic task practice targeting core stability with a focus on minimising upper-limb weight bearing to improve engagement within daily tasks, balance and gait.
- Education around optimal activity and exercise tailored to each individual and their lifestyle.
- Exploring meaningful and enjoyable physical activity to maximise functional outcomes and active participation in the longer-term management of their condition.
- Signposting to local services such as: exercise on prescription schemes; Ataxia UK and utilisation of smartphone applications.
- Exploring barriers to physical activity and exercise participation. Often individuals express lack of confidence due to balance or motivation to attend local/virtual activities and/or classes that would be appropriate for someone with ataxia.
- Compensatory approach with consideration of exploring the use of orthotics or devices to maximise independence.

Occupational Therapy

Using skills of task analysis, an OT is able to break down individual tasks into its component parts to identify how the person's ataxia is impacting on performance. This informs education, coaching of alternative techniques to change the approach to the activity or selection of adaptive aids. It is vital that OTs focus on activities that are important and meaningful to the person with ataxia. Measurement of satisfaction is used to demonstrate effectiveness of occupational therapy intervention in people with progressive ataxias [6,8]. For example, initial intervention for feeding incorporates coaching of proximal stabilisation techniques and trial of weighted cutlery, although the evidence for weighted tools is low. As the condition progresses, the person might become dissatisfied with their performance when feeding and rely on someone else to feed. The introduction of assistive devices, such as the manual neater eater, can help to maintain independence and reduce reliance on others, with subsequent improvement in satisfaction levels. Psychological adjustment to a person's increasing disability needs careful consideration throughout the person's treatment. Interventions might include:

- Fatigue management education: balance of rest and activity, addressing poor quality sleep, use of relaxation techniques
- Task adaptation and techniques focusing on optimising postural stability and promoting normal movement to increase the chances of success
- Assessment of hand function and intervention to optimise function and maintain range of movement
- Equipment provision including assistive technologies
- Addressing environmental barriers to participation.

Speech and Language Therapy

Like many other disciplines there is currently limited evidence for clinically effective treatments for SLTs in ataxia. Patients living with ataxia may experience changes to their speech and voice [10]. Evidence is growing for exercises targeting control of volume, tremor in the voice, pitch fluctuations and slurring of speech [10]. This impacts a person's ability to participate in meaningful conversations and engage in vocational and leisure activities. Dysphagia (swallowing difficulties) is also a common symptom of ataxia [17]. Difficulties may include difficulties in chewing food and coordinating movements for swallowing which can result in a feeling of food sticking in the throat, as well as coughing and spluttering when eating and drinking. This can lead to embarrassment, discomfort, compromise of chest health (due to food/drink entering the airway) and withdrawal from social situations [15].

The role of the SLT is to educate patients on how ataxia impacts speech, voice and swallowing ability. An in-depth assessment of the speech, voice and swallowing systems is completed. Interventions may include:

- Strategies for safe swallowing such as safe positioning for mealtimes
- Use of adaptive equipment including rate-controlled cups
- Modification of diet or fluids
- Strategies for clear speech
- Exercise-based intervention to improve and maintain speech and voice output.

Initiatives during COVID-19 Pandemic

During the pandemic there were longer waiting lists and an increase in referrals for all disciplines at NHNN for patients living with ataxia. We hypothesise that this was secondary to national lockdowns affecting the ability of community services to access patients; self-isolating and shielding staff, temporary cessation of 'non-urgent' services and redeployment of staff [9].

Initiatives were undertaken at NHNN to ensure patients were still able to access treatment and intervention.

1. Telehealth clinic

In March 2020 in the first wave of the COVID -19 pandemic, MDT clinics were converted to telehealth appointments. This proved to be a very effective way of managing this patient group, allowing more patients to access the service whilst being able to isolate at home. All patients that attended the telehealth MDT Ataxia Clinic from January-May 2021 were contacted. 16/30 responded and took part in a retrospective telephone survey. 13/16 (81%) patients reported an overall positive experience of which 11 (69%) would recommend to others. Benefits reported included reduced costs and carer burden associated with travel and ease of access at home. Some felt their needs may have been better met in person as they felt physical assessment might have been beneficial. This clinic continues to offer virtual consultations and face-to-face for appropriate patients.

2. Exercise and education group

Reduced exercise tolerance and deconditioning became more commonly reported patient symptoms. Therefore, a virtual education and exercise group was created, comprising of 6-8 patients, which ran weekly for one-hour over a four-week period. Patients were initially assessed for the group in a 1:1 consultation and self-efficacy and activity levels were measured through patient reported outcome measures before and after the course. This data is currently being reviewed, however patients reported enjoyment of exercising in a group format and increased motivation to engage in sustained exercise activity outside of the group. The group continues to run on a quarterly basis.

3. Motor speech group

To capture patients unable to access local communication services, a virtual group was set up to address the main speech and voice challenges faced by people with ataxia. This novel approach targeted the principles of 'smooth and steady' speech and voice production. The group comprised of 3-6 patients, seen for one-hourly, weekly sessions over six weeks. Each patient had a 1:1 initial virtual consultation where communication and QOL were measured. The initial feedback from three pilot groups was very positive, specifically; feeling more confident, enjoying access from their home, particularly as many lived outside of London, and feeling a sense of connectedness with others who have similar communication challenges. Outcome measures also demonstrated improved speech intelligibility as rated by unfamiliar listeners. Due to their success, and lack of availability of this type of service in the community, these groups continue to run at NHNN.

Evaluation of the outcomes of practice

- The above practices and the MDT ataxia clinic have seen positive outcomes in patients. This is based on survey results and anecdotal evidence.
- Improved regular participation in exercises and activity has resulted in reduced re-referral rate to NHNN services.
- Improved understanding of each individual's condition and access to support networks.
- Improved mood.
- Confidence with the utilisation of self-management strategies to optimise and maintain function and increase independence.
- Empowerment of carers/family members to support people to follow tailored programmes provided by Allied Health Professionals.
- Sense of belonging when engaging in a group exercise environment.

Conclusion

People living with ataxia experience a plethora of symptoms. Despite the absence of disease-modifying treatments for most ataxias, many aspects of these disorders are treatable, and it is essential that healthcare professionals know how to optimise symptom management. Specialist MDT assessment and management as well as the development of individualised, tailored treatment approaches is therefore vital. Current recommendations on the management of these conditions are largely based on clinical experience and anecdotal evidence, hence the importance of further research. The Covid-19 pandemic has created opportunities of continued patient access to therapy intervention to maintain function, ensure safety and support psychosocial wellbeing. During this time NHNN therapies were able to offer novel approaches to intervention via telehealth which demonstrated positive patient outcomes.

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Neuroliteratur: David Ferrier (1843-1928)

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Introduction

However great their achievements in clinical neurology and investigative neuroscience, however loud their acclamation by their peers, few if any neurologists become sufficiently famous (or infamous) to impinge on the wider public consciousness, certainly not to the point of becoming subjects for comment in popular fiction.

The only example that initially springs to my mind is the "Penfield mood organ" described in Philip K. Dick's (1968) novel *Do androids dream of electric sheep*? (on which the 1982 film *Blade Runner*, a very different cultural artefact, was based), which is surely a reference to Wilder Penfield (1891-1976), whose work stimulating the cortex of awake epilepsy patients undergoing surgery allowed him to map the functions of various regions of the brain [1]. In contrast, I am aware of three literary works which either mention by name [2], or respond to the experimental work of [3], David Ferrier (1843-1928), perhaps Penfield's ultimate precursor in the field of brain stimulation studies.

Background

David Ferrier (Figure 1) first came to prominence in the medical profession as a consequence of his experimental studies commenced in 1873 at the West Riding Pauper Lunatic Asylum in Wakefield, West Yorkshire [4,5]. Using faradic current to stimulate points on the cerebral cortex of various animals, he was able to evoke predictable motor responses from certain locations, emphasising the complex goal-directed nature of the movements observed. Lesions of the same regions produced corresponding motor deficits. In his experimental studies, Ferrier was explicitly seeking to provide support for the clinical inferences on cortical localisation made by John Hughlings Jackson (1835-1911).

Ferrier's "initial publications caused an immediate sensation [6]" as did his experimental demonstrations at meetings of the British Medical Association and the British Association for the Advancement of Science in 1873. By the middle of the year, he had extended his work to monkeys, these findings later presented at the Royal Society in 1874 and 1875. His studies resulted in a monograph, *The functions of the brain*, published in 1876, and in that year he was elected a Fellow of the Royal Society.

Experimental studies such as those of Ferrier had been one of the factors prompting the development of a vocal anti-vivisection movement in the latter half of the 19th century [7]. Lobbying, particularly by the group known as the Victoria Street Society, in which Frances Power Cobbe (1822-1904) was a prominent member, lead to the passing of the Cruelty to Animals Act in 1876, requiring experimenters to hold a licence issued by the Home Office in order to perform their investigations. The founding of the Physiological Society in 1876, with Ferrier one of the initial members [8], was at least in part a response to this possible threat to the continued practice of experimental animal studies.

Despite Ferrier's findings, the issue of cortical localisation (motor centres) was still disputed by some, a matter which came to a head in a debate held at the International Medical Congress in London in August 1881. The German physiologist Friedrich Goltz (1834-1902) demonstrated dogs without motor weakness despite what he claimed was complete destruction of the cerebral cortices, whereas Ferrier demonstrated a monkey rendered hemiplegic by a focal experimental brain lesion. Ferrier had previously been critical of, if not frankly scathing about, Goltz's experimental method ("fatal objections") in his Gulstonian Lectures of March 1878 on *The localisation of cerebral disease* delivered at the Royal College of Physicians [9]. Subsequent independent neuroanatomical studies of the experimental animals of both researchers indicated that Goltz's lesions were not as extensive as he had imagined, and hence the argument for localisation presented by Ferrier proved the scientific victor [10,11]. However, it was this public demonstration which formed the basis for Ferrier's subsequent prosecution, instigated by the anti-vivisectionists, under the Cruelty to Animals Act 1876, charged with not having an appropriate licence for performing such experiments.

The issue became a public and professional cause célèbre, the British Medical Association paying Ferrier's legal fees and its lawyers representing him in court. Commentary on the trial and its ramifications appeared not only in the medical and scientific journals but also in the national and international press. Ferrier was acquitted when it became known that his colleague at King's College London, Gerald Yeo, had performed the surgery for which he had the appropriate licence under the Act [12].

No doubt it was this legal entanglement which brought Ferrier sufficiently within the public gaze to prompt his appearance [2], and/or the thematic use of vivisection [3], in works of literature, some of which have subsequently been cast as "retrials" [3] of Ferrier. (Spoiler alert: In the following discussion of these three works, some plot details are made explicit.)

Wilkie Collins: *Heart and Science: A story of the present time* (1883) [13]

Written shortly after Ferrier's prosecution (the subtitle is surely significant in this respect), this work has been generally acknowledged to be as much a protest against vivisection as a novel [2,3], although personally I find it has a pantomimic, sub-Wildean, comedic charm to it. It is known that Collins was a personal friend of Frances Power Cobbe, one of the chief anti-vivisection activists, and she is thanked in the first of the two prefaces to the novel.

Ferrier is specifically referenced in the second preface, addressed "To Readers in Particular":

> *… a supposed discovery in connection with brain disease, which occupies a place of importance [in the novel], is not (as you may suspect) the fantastic product of the author's imagination. Finding his materials everywhere, he has even contrived to make use of Professor Ferrier – writing on the "Localisation of Cerebral Disease," and closing a confession of the present result of post-mortem examination of brains in these words: "We cannot even be sure, whether many of the changes discovered are the cause or the result of the Disease, or whether the two are the conjoint results of a common cause." Plenty of elbow room here for the spirit of discovery.*

> *One of the characters in the novel, Dr Nathan Benjulia, an Oxford graduate, conducts experiments on monkeys and dogs in his laboratory, which has no windows and a skylight with a white blind inside, to try to understand a brain disease (not specified). In her analysis of the novel, Laura Otis has likened Benjulia's "tickling" of the spine of one of the female characters, ten-year old Zo (Zoe), in which he claims he touches the cervical plexus (Chapter XII), to Ferrier's brain-mapping experiments, arguing that the correlation between a nervous stimulus and a specific movement in both instances suggests that Collins did read Ferrier's work [3].*

Figure 1: David Ferrier. Source: Wellcome Collection (https://wellcomecollection.org/works/cqps5h8w) Public Domain Mark (PDM) terms and conditions https://creativecommons.org/publicdomain/mark/1.0

The source of the quotation, not specified in Collins's text, is from Ferrier's Gulstonian Lectures of 1878 [14]. It appears again, in the text of the novel, near its climax, ascribed to a "celebrated physiologist" (Chapter LIX), a fair description of Ferrier by 1883.

One of the characters in the novel, Dr Nathan Benjulia, an Oxford graduate, conducts experiments on monkeys and dogs in his laboratory, which has no windows and a skylight with a white blind inside, to try to understand a brain disease (not specified). In her analysis of the novel, Laura Otis has likened Benjulia's "tickling" of the spine of one of the female characters, ten-year old Zo (Zoe), in which he claims he touches the cervical plexus (Chapter XII), to Ferrier's brain-mapping experiments, arguing that the correlation between a nervous stimulus and a specific movement in both instances suggests that Collins did read Ferrier's work [3]. But, as we all know, correlation is not causation and personally I am doubtful that Collins was able to engage in any depth with Ferrier's scientific publications rather than with the reports of them in the popular press or in anti-vivisectionist propaganda. However, Benjulia does later admit that when vivisecting a sick monkey, obtained from the zoological gardens, he thought of the child when hearing the animal's cries of suffering (Chapter XXXII).

Otis argues that the novel reiterates the central questions of Ferrier's trial, particularly the question of who is to police the performance of experimental scientific work [3]. Jessica Straley has seen the novel as Collins's reflection on the connection between scientific and literary practices, both potentially shocking and sensationalist [15]

HG. Wells: *The island of Doctor Moreau* (1896) [16]

Although Ferrier is not mentioned by name in Wells's novella, it has been argued that this work invokes Ferrier's research and that, like Collins, Wells enacts a "retrial" of Ferrier [3]. Certainly Wells had some scientific education, some of his teaching coming from Thomas Henry Huxley (1825-1895) in the mid-1880s at the School of Science in South Kensington (viii). It is possible that, somewhat earlier, around 1872, Ferrier was one of the demonstrators in Huxley's classes at South Kensington [17].

The title character of the novel is a vivisector, working in isolation on a volcanic island located somewhere in the Pacific Ocean. The locked enclosure where he performs his experiments is described as a "laboratory" (97,105). Moreau explains to the shipwreck survivor, Edward Prendick, the novel's apparent narrator, that he is committed to the "study of the plasticity of living forms" (71). Taking a gorilla, he had operated to make his "first man", finding that "it was chiefly the brain that needed moulding" (76). The resulting chimerical experimental forms, the "Beast-Folk," inhabit the island.

Prendick's disappearance is dated to 1887-8 (5-6), and whilst Moreau dates his work back 20 years (77) he and his associates have been on the island for only about ten or eleven years (11,19,75,106), when they were "howled out of the country [England]". This chronology indicates that they left London around 1876, late enough to know of Ferrier's initial publications but prior to his prosecution.

Having some scientific training himself, indeed with Huxley (29), Prendick is not unsympathetic to experimental science, yet he is revolted by the programme pursued on the island: "Had Moreau had any intelligible object I could have sympathized at least a little with him" (95).

Bram Stoker: *Dracula* (1897) [18]

Few novels can have achieved the cultural reach of Bram Stoker's fin-de-siecle novel, so no recapitulation of the plot is necessary here. However, a perhaps less well-remembered allusion occurs in the following passage:

> *Men sneered at vivisection, and yet look at its results today! Why not advance science in its most difficult and vital aspect – the knowledge of the brain? Had I even the secret of one such mind – did I hold the key to the fancy of even one lunatic – I might advance my own branch of science to a pitch compared with which Burdon-Sanderson's [sic, with hyphen; incorrect] physiology or Ferrier's brain-knowledge would be as nothing (80).*

The quotation purports to be from the diary of Dr John Seward, a clinician who, aged twenty-nine, has a lunatic asylum "all under his own care" (63). This location may be significant in view of the fact that Ferrier's original publications were, as mentioned, based on experimental researches performed at an asylum, the West Riding Pauper Lunatic Asylum, where laboratory space and experimental animals had been provided for him by Dr James Crichton-Browne, appointed asylum superintendent at the age of twenty-five [4,5]. Seward himself does not perform any animal experimentation in the novel, and his studies of the zoophagous patient, Renfield, seem unresolved.

The passage cited is also quoted (with ellipsis) as one of the chapter epigraphs in Terrie Romano's book on John Burdon Sanderson (1828-1905) (sic, no hyphen; correct) [19], the nineteenth century physiologist and administrator who may have been one of Ferrier's early supporters. It may be the case that he encouraged Ferrier to move to London in 1870 [20], and that Ferrier worked for or with him at the Brown Animal Sanatory Institution in London in the early 1870s. Certainly Burdon Sanderson communicated Ferrier's papers on cerebral stimulation in monkeys to the Royal Society in 1874 and 1875 (as Ferrier was not then FRS) and the initial meeting of what was to become the Physiological Society was held in his house in London in 1876.

In the notes to both the Penguin Classics edition and the Oxford World's Classics edition of Dracula, Burdon Sanderson's inappropriate hyphen is repeated, but more worryingly Oxford World's Classics misdates Ferrier's birth as 1847, rather than 1843 [21], and even more astonishingly Penguin Classics interprets "Ferrier" as James Frederick Ferrier (1808-1864), a Scottish

metaphysician (444). From the context alone this attribution cannot be correct. Furthermore, even if there were any doubt, a later incident in the book surely confirms the reference to be to David Ferrier. The asylum patient Renfield is found collapsed in his cell with a right-sided paralysis (although he can still deliver an eloquent monologue, pertinent to the plot!):

> *The real injury was a depressed fracture of the skull, extending right up through the motor area. … "The whole motor area seems affected. The suffusion of the brain will increase quickly, so we must trephine at once or it may be too late." (294)*

The concept of a "motor area" in the brain relates directly to the clinical work of Hughlings Jackson and the experimental work of Ferrier. Stoker had written to his older brother, Thornley Stoker (1845-1912), an anatomist and surgeon who from 1876 held the chair of anatomy at the Royal College of Surgeons in Ireland, for information on the effects of skull injury and his notes for Dracula include a detailed response with a sketch of a man's head indicating the various effects of damage to different parts of the skull (451).

It may be noted that another neurologist is also mentioned in Dracula: Jean-Martin Charcot (1825-93). Seward accepts that Charcot has proved hypnotism "pretty well" (204), and its repeated use later becomes an important plot element in the pursuit of Count Dracula. With respect to Charcot, Ferrier dedicated his 1878 book of the Gulstonian lectures to him, and probably encountered him at the 1881 International Medical Congress in London, where the hemiplegic monkey demonstrated by Ferrier apparently provoked from Charcot the comment "C'est un malade!"

Discussion

Ferrier's work, and more particularly its reception in lay as opposed to professional circles and discourses, influenced at least three writers in the later nineteenth century. Wilkie Collins was vigorously opposed to vivisection; Wells was tentatively in favour. Pedlar argues that Stoker is equivocal about science [2]. Then, as now, vivisection and "vivisectors" remain emotive subjects, calling forth responses not only from within but also from outside their particular fields of scientific study.

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Neurology: A Clinical Handbook

Author: Charles Clark
Published by: Wiley
Edition: 6th, 2022
Price: £49.99
Pages: 496
ISBN: 978-1119235729
Reviewed by: Rhys Davies, MA BMBCh (Oxon), PhD (Cantab), MRCP (London).

Reviewing Dr Charles Clarke's book may well have been my first experience of reading, cover to cover, a neurology text book during what is (undeniably by now) the second half of my career as a neurologist. As such, I approached the task with trepidation!

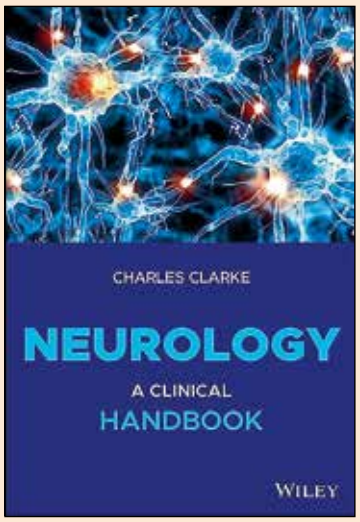
I need not have worried. The work was onerous neither in its nature nor its duration. The book is short and the reader benefits from clear writing and from having to pause very rarely to reflect upon perceived omissions or controversial comments. Although by way of providing reassurance that your reviewer read every page, I can confirm that the unstable spelling of a mammillary did not go unnoticed (the third 'm' was sometimes left out).

The overall structure is sensible and of course follows that of the comprehensive Queen Square textbook, co-edited by Charles Clarke. Some nice e-resources are highlighted.

As a handbook, the intention is to cover core topics and these are chosen with the wisdom to be expected of the author's years' experience as a clinician. Looking for things to which I myself might have given greater prominence, I might mention the chronic low CSF pressure state as a cause of brain or cord deficits even without headache (not so uncommon, easily missed on conventional tests and also amenable to treatment). The state of CNS ischaemia from a dural AV fistula might be another.

Conversely there is a generous two-page spread for neurology at altitude. Of course, this issue features infrequently in UK practice but is handled so authoritatively that it is well worth its space. And of course we shouldn't forget that books written in the UK may be read elsewhere, even near to (or upon) high mountains.

In summary, this would be a handy textbook for a player in the first 'minutes' of the neurology game wanting an overview, or a player further into the first half who might need a quick reference. For second-half players it may provide reassuring perspective in areas of practice not encountered so frequently, or a resource for double-checking one's instincts in preparation for some general teaching.



The Sleeping Beauties: And Other Stories of Mystery Illness

Author: Suzanne O' Sullivan
Published by: Picador
Price: £10.99
Pages: 336
ISBN: 978-1529010572
Reviewed by: Timothy Boey, Medical Student, University of Liverpool, UK.

Suzanne O'Sullivan's book on functional neurological disorders is written with the aim of sharing her experiences with patients suffering from perceived mysterious illnesses, and shedding light on their pathogenesis. It is written for the general public to enjoy but, for me, being in possession of undergraduate level medical knowledge of clinical neuroscience, gave some useful context.

Written in a first-person narrative format, Dr O'Sullivan describes in chronological order her visits to different corners of the world and the patients she meets. Each chapter is divided according to the instance of functional neurological disorder that she encounters, with a bit of humour and is mostly self-contained. Rich descriptions are given for each destination and each patient interaction; expansive explanations of pathogenesis are provided with the links to social, economic, psychological, and biological factors. Her clinical reasoning is laid out plainly and the clinical examinations are explained for the uninitiated, and the partially initiated!

Although separated by chronology, the author links the chapters together through building on previously established explanations and with progressively more nuance. Previously touched upon concepts are revisited in a way that adds resonance, without intrusive repetition. While psychosocial models and theories were referenced occasionally throughout the book, the student in me might have preferred more original referencing and specification of the various media sources.

As to the psychosocial models and biological explanations, quite convincing explanations are given for the pathogenesis of functional neurological disorders, albeit without scientific verification. Furthermore, in arguing that there is bias in disease parameter definitions, the author does not acknowledge the myriad of established epidemiological data that inform such definitions and tends to make light of possible pre-disease states. As a student of medicine (including neurology), I would have liked more on potential public health opportunities.

Overall, The Sleeping Beauties: And Other Stories of Mystery Illness, provides an intriguing and informative read on functional neurological disorders, providing the author's personal explanation, alongside links to socioeconomic factors. It's definitely an enjoyable read, and useful for me (and for my fellow students/trainees) in trying to synthesise a truly complex but essential part of medicine. Of course, it isn't a textbook, or a science tome, and shouldn't be read as one.

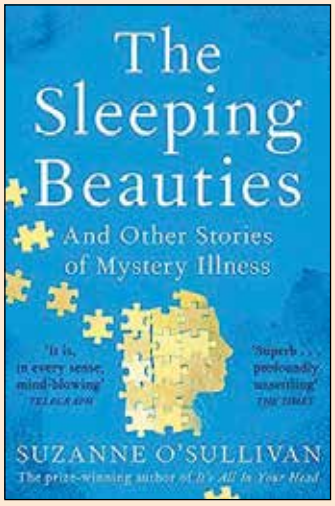


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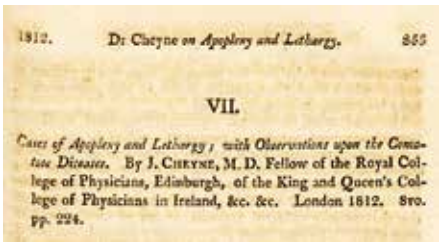
Figure 1. John Cheyne



1812. Dr Cheyne on Apoplexy and Lethargy. 853

VII.

Cases of Apoplexy and Lethargy; with Observations upon the Comatose Diseases. By J. Cheyne, M.D. Fellow of the Royal College of Physicians, Edinburgh, of the King and Queen's College of Physicians in Ireland, &c. &c. London 1812. 8vo. pp. 224.

Figure 2. Cheyne on apoplexy and lethargy

The fine scholar-physicians of the 17th and 18th centuries, who included Robert Whytt, John Cheyne, Thomas Sydenham and Thomas Willis, made meagre distinction between physical and emotional symptoms. They recognised both but viewed them as essential manifestations of nervous disorders. One ominous physical sign first recognised by John Cheyne was of abnormal breathing: *Cheyne-Stokes respiration*. It bears the eponyms of Cheyne and William Stokes who gave a later account (q.v.).

Physicians who care for emergencies frequently encounter Cheyne-Stokes respiration: abnormal breathing, in which cycles of apnoea alternate with series of gradually increasing depth and frequency of breathing. It is often sinister.

In 1818, John Cheyne (Figure 1) described a sixty-year-old man, a sufferer from gout who complained of palpitations and pain in the chest and had fallen from a chair but could not remember doing so. He found:

> *An extremely irregular and unequal pulse on examination, and the patient was confused and had headache. Following blood letting and the use of leeches, he improved. On the 10th of April he was found in bed, speechless, and hemiplegiac… The only peculiarity in the last period of his illness, which lasted eight or nine days, was in the state of the respiration. For several days, his breathing was irregular; it would cease for a quarter of a minute, then it would become perceptible, though very low, then by degrees it became heaving and quick, and then it would gradually cease again. This revolution in the state of his breathing occupied about a minute, during which there were about thirty acts of respiration [1].*

He diagnosed apoplexy "that must have depended upon increased action of the vessels of the head." At post mortem was found a left cerebral infarct. The heart was three times larger than normal, the left ventricle greatly enlarged, the right ventricle converted into a soft fatty substance…Aorta steatomatous.

John Cheyne (1777-1836) was the son of a surgeon. He is not to be confused with his namesake George Cheyne (1671-1743) who in 1733 composed a famous volume, The English Malady, which related to Nervous Distempers, Vapours, and Lowness of Spirits, then widely considered hysteria.

At the age of thirteen, John Cheyne began to attend to his father's poor patients. He had to supply them with medicines, to bleed them, and to dress their wounds; thus he acquired an early familiarity with diseases. He graduated in medicine at the remarkably early age of eighteen at Edinburgh [2]. Alexander Monro secundus (1733-1817), who described the interventricular foramen, was one of his tutors, and Charles Bell taught him pathology and dissection. After four years of military service, he practiced with his father in Leith from 1799.

In 1809 he moved to Dublin where he was appointed physician to the Meath Hospital and Professor of Medicine at the College of Surgeons. He subsequently became Physician-General in the Irish army in 1820, the highest medical ranking in Ireland. He was a founder of the Dublin Hospital Reports. He wrote books on the croup, and Essays on Diseases of Children. In An essay on hydrocephalus acutus, or dropsy in the brain (1808), he recorded 23 cases; all but six succumbed: the suspected cause was tuberculous meningitis. In Cases of Apoplexy and Lethargy: With Observations Upon the Comatose Diseases (1812) (Figure 2), he distinguished subarachnoid from intracerebral haemorrhage, probably the first physician to provide an illustration of subarachnoid hemorrhage:

> *For the most part, extravasated blood is found within the cranium, **sometimes between the membranes**, sometimes in the substance of the brain. [my emphasis]*

Another of his most important works was considered that on the typhus epidemics which ravaged Ireland. Pettigrew's Biographical Memoirs (1839) provided a lucid, detailed account of his medical life [3].

Cheyne was elected a Fellow of the Royal Society of Edinburgh in 1814. After a distinguished and productive career, ill health caused his return to England, where he settled on a country estate in Sherrington, near Newport-Pagnell, Buckinghamshire in 1831. His last book, Essays on Partial Derangement of the Mind was published in 1843, seven

> *"Physicians who care for emergencies frequently encounter Cheyne-Stokes respiration: abnormal breathing, in which cycles of apnea alternate with series of gradually increasing depth and frequency of breathing. It is often sinister.*

Figure 3. Cheyne's monument

examples of that disease. The symptom in question was observed by Dr. Cheyne, although he did not connect it with the special lesion of the heart.' It consists in the occurrence of a series of inspirations, increasing to a maximum, and then declining in force and length, until a state of apparent apnœa is established. In this condition the patient may remain for such a length of time as to make his attendants believe that he is dead, when a low inspiration, followed by one more decided, marks the commencement of a new ascending and then descending series of inspirations.

Stokes: The Diseases of the Heart and the Aorta. p.340

years after his death in 1836 – perhaps an abreaction from his own late-life depression. The cause of death was 'Mortification of the Lower Body'. A modest, diffident, and religious man he left detailed instructions for his burial:

> *My funeral must be as inexpensive as possible: let there be no attempt at a funeral sermon. I would pass away without notice from a world which, with all its pretensions, is empty.*

A large stone monument (Figure 3) commemorates him.

Thirty-six years after Cheyne's account, the illustrious William Stokes (1804-1878) [4] in one of many highly regarded texts acknowledged Cheyne's earlier account [5]. Stokes's father had succeeded Cheyne as Professor of Medicine and was a friend of Robert Graves René Laennec, and the young Oscar Wilde [6]. William Stokes described a disorder of the pattern of respiration, not caused by a lung condition, but by an enfeebled heart, due to fatty degeneration of this organ or other causes [7]. "This symptom…I have only seen during a few weeks previous to the death of the patient…" [7]. Stokes noted disease of the aortic valve was common. He is also renowned for his account of Stokes-Adams attacks [8].

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Dizziness and Balance Workshop

Conference details: 8 December, 2022, London Transport Museum, London, UK. ***Report by:*** Dr Maria Francisca Rocha, IMT 2 trainee. ***Conflict of interest:*** None declared.

The Dizziness and Balance Workshop returned in 2022 as a one-day conference aimed at those with an interest in the management of acute dizziness and balance disorders. The workshop was held on 8th December at the London Transport Museum and featured a series of lectures delivered by worldwide leaders on the subject.

The workshop built upon the legacy of previous years and was highly subscribed by a diverse range of healthcare professionals, including emergency department clinicians, physiotherapists, nurses, junior doctors, and general practitioners. The workshop focused on the management of acute vertigo and aimed to introduce attendees to the fundamentals of acute peripheral and central vestibular disorders.

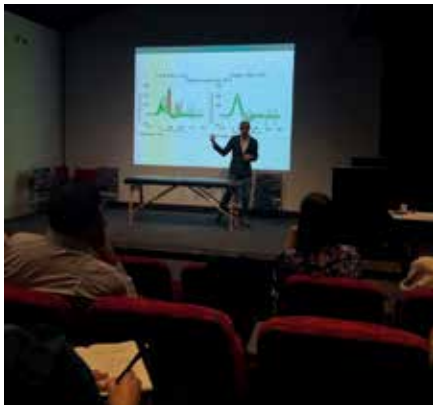
The day began with the "Differential diagnosis of the dizzy patient" by Professor Diego Kaski who highlighted the importance of a detailed clinical history and examination in order to arrive at an accurate diagnosis. Professor Kaski went on to a second talk on vestibular neuritis and labyrinthitis discussing the pathophysiology, diagnosis, and management of these disorders. He also discussed the various treatment options for vestibular neuritis and labyrinthitis, including the use of corticosteroids and vestibular rehabilitation.

This was followed by a presentation by Mr. Darren Whelan on "Instrumented Assessment for Acute Vertigo", discussing the range of tools and techniques available for the assessment of acute vertigo, including video-oculography and caloric testing. He highlighted the importance of a comprehensive vestibular assessment in cases of acute vertigo.

Professor Louisa Murdin gave a succinct and practical lecture on vestibular migraine, discussing the clinical presentation, diagnosis, and treatment options for this disorder. She highlighted the importance of a detailed clinical history and examination in making an accurate diagnosis and discussed the various pharmacological and non-pharmacological treatment options for vestibular migraine and the important role dizziness plays.

The next presentation was on "Acute Vertigo - when is it a stroke" by Professor Adolfo Bronstein, exploring the differential diagnosis of acute vertigo, and the importance of early recognition of stroke. He highlighted the various clinical features that can help distinguish stroke from other causes of acute vertigo and discussed the potential pitfalls of relying solely on examination.

Throughout the day, there were several practical workshops held that provided attendees with an opportunity to practice their skills and learn new techniques. The first workshop comprised of BPPV and Dix Hallpike manoeuvres with the discussion of the various treatment options for BPPV, including the use of canalith repositioning manoeuvres. The second workshop was on distinguishing central from peripheral vertigo and the use of video Head Impulse Test (vHIT). The third workshop involved the demonstration of various techniques for the assessment of balance and gait.



Attendees engaged in discussions and debate, some of the key themes that emerged included the importance of a multidisciplinary approach in the management of acute dizziness and balance, the need for more research into the pathophysiology and treatment of vestibular disorders, and the challenges of diagnosing and managing complex cases.

The Dizziness and Balance Workshop 2022 was a highly engaging day that provided attendees with an overview of the principles of acute peripheral and central vestibular disorders, synthesised for the non-specialist practitioner, and with clear practical take-home messages and opportunities for skill development. The workshop was a great success, and we look forward to the next one.

National Musculoskeletal and Pain Medicine Course

Conference details: 8-10 February, 2023, University of Leeds, UK. ***Report by:*** Dr Ismail Abdulfattah Ibrahim MBBS, MRCP, FWACP (Rheumatology), EULAR cert Rheumatic Diseases. ***Conflict of interest:*** None declared.

The National Musculoskeletal and Pain Medicine Course organised by the University of Leeds and the British Society of Physical and Rehabilitation Medicine (BSPRM) was the first face-to-face course organised by the society post-pandemic. It was held at the University of Leeds, UK between the 8th and 10th of February 2023. The multi-speciality nature of musculoskeletal (MSK) medicine meant that experts in clinical and research aspects of MSK and rehabilitation were naturally attracted to the course both as attendees and as presenters. It focused extensively and effectively on the theoretical bases of MSK and Pain Medicine combined with practical workshops aiming at developing the skills of trainees and clinicians.

The course was formally opened with a welcome address by Professor Rory O'Connor, Professor in Rehabilitation Medicine in Leeds and Dr Manoj Sivan, the President of BSPRM and Associate Clinical Professor in Rehabilitation Medicine. They explained the relevance and significance of MSK competencies in Rehabilitation Medicine practice and other relevant specialties in the UK and internationally.

Presentations on the first day were divided according to regional anatomy. Dr Marwan Al-Dawud, a Sports and Exercise Medicine Physician with a special interest in Tendinopathies and MSK ultrasound and intervention therapy discussed the applied anatomy of the shoulder, its common pathologies and rehabilitation principles. Following this, Dr Piera Santullo, a Rehabilitation Medicine Consultant at Nottingham University Hospitals NHS Trust, UK, delivered a presentation on the applied anatomy, common pathologies and rehabilitation principles of the elbow. Conditions such as carpal tunnel syndrome, de Quervain's tenosynovitis and other hand and wrist pathologies were discussed by Dr Richard Wakefield, a Senior Lecturer in Rheumatology in Leeds with special interest in MSK ultrasound and ultrasound guided injections.

Participants felt rejuvenated and refreshed following a tea break, consequently making the time well suited for the practical workshops on anatomic and ultrasound techniques for diagnoses and interventions in pathologies of soft tissues and joints of the upper limbs. The workshop session was very practical, hands-on, extremely inspiring and timely for clinicians and trainees. It could have been prolonged because of the interest and enthusiasm of participants had the lunch not arrived, bringing the morning session to an end.

The afternoon session focused on lower limb conditions. Dr Javvad Haider, Consultant Rehabilitation Medicine Physician in Cardiff did justice to relevant anatomy, MSK pathology and rehabilitation management of the hip joint. Next were conditions relating to the knee, ankle and foot, presented in a very simplified and interactive manner by Dr Samuel Thistleton, Consultant in Sports and Exercise Medicine. These theoretical sessions were followed by very educational practical ultrasound sessions on lower limb structures by the speakers. Dr Gui Tran, a Rheumatologist with an interest in MSK Medicine, delivered an interesting interactive session on inflammatory and autoimmune conditions including gout, rheumatoid arthritis, and polymyalgia rheumatica.

The second day started with another presentation by Dr Haider on applied anatomy, common conditions and rehabilitation principles in management of the spine. This presentation focused on biomechanics in general and how it affects the spine. Spinal segmental/somatic dysfunction and a practical workshop on how to examine for it was another excellent highlight of the second day, delivered by Dr Martyn Speight, a foremost and renowned expert in medical osteopathy, and Musculoskeletal & Sports Physician.

After a tea break, Dr John Titterington, Consultant in Pain Medicine at Leeds Teaching Hospital delivered a presentation on percutaneous interventional injections for radiculopathy such as caudal blocks, selective nerve blocks, nucleoplasty and the use of an implantable stimulator. Osteoporosis was succinctly presented by Dr Sunil Nedungayil, a General Practitioner with special interest in MSK, and Associate Medical Director in the Northern Bone Health project. Following this, Dr Ece Yilmaz-Kara, Consultant in Physical and Rehabilitation Medicine in Reading, UK, discussed soft tissue release techniques relevant to MSK and rehabilitation medicine along with a hands-on session on acupuncture needles in dry needling techniques and trigger point injections. Dr Moheb Gaid, Consultant in Rehabilitation Medicine, shared his extensive experience and expertise on the use of diagnostic/therapeutic nerve blocks in complex spasticity management.

In the afternoon session, delegates attended a magnificent motion analysis laboratory in the University of Leeds Faculty of Biological Sciences where Sarah Astill, Associate Professor in Motion control along with her PhD students welcomed participants to the afternoon session. Dr Kitty Tang, a clinical scientist in Leeds Teaching Hospitals NHS Trust, discussed the basics of motion analysis, kinematics, and its relevance to neurological conditions. The description of the second day wouldn't be complete without mentioning the evening social event. Delegates and organisers were treated to a nice dinner which further facilitated networking and socialisation, much needed after the pandemic.

The third day began on an aerobic mode, with Exercise Prescription discussed by Dr Ai Lyn Tan, Associate Professor in Rheumatology and Director of Research and Innovation at Leeds. Participants were also signposted to beneficial sites including Moving Medicine, Versus Arthritis, parkrun Practice and the use of the FITT and ABC principles of exercise prescription. Dr Manoj Sivan discussed the pathophysiology of pain and the approach to management of acute and chronic pain. This served as a very good prelude to the topic presented by Dr Jo Corrado, ST5 Rehabilitation Medicine Trainee in Leeds, who discussed Chronic Fatigue Syndrome and Fibromyalgia, explaining the commonalities, exploring dysautonomia and its role in these conditions and possibly in Long COVID based on her research experience.

After the tea break, Dr Sheila Black, Consultant in Pain Medicine and Regional adviser for Pain Medicine in Yorkshire, UK, delivered a comprehensive presentation on neuromodulation. Dr Rohit Bhide, Consultant in Spinal Injuries and Amputee & Prosthetics Rehabilitation at Sheffield Teaching Hospitals NHS Foundation Trust, delivered a talk on a structured pathway for pain management in amputee patients with focus on neuroma management. The delegates then had ample time for more hands-on revision sessions on ultrasound techniques. The last session for the course was the icing on the cake. Dr Abayomi Salawu, Consultant in Rehabilitation Medicine at Hull University Teaching Hospital and Honorary Reader with Hull/York Medical School, discussed the topic 'skeletal muscle as an endocrine organ'. He explored the basic physiology of skeletal muscle and its clinical relevance. He ended the talk by discussing 'Exercise is Medicine,' emphasising the danger of physical inactivity to our patients and the global economy.

Dr Sivan and the faculty thanked all delegates and organisers for attending and making the course a huge success with positive feedback throughout the 3 days. They spoke about encouraging new brains to further MSK and pain rehabilitation in the UK and internationally, while urging trainees to engage in hands-on practice and integrate MSK into every aspect of rehabilitation medicine practice. Course group pictures were taken, and delegates departed feeling very fulfilled.

RCPsych Faculty of Neuropsychiatry Annual Conference 14-15 September 2023 RCPsych London/Live streamed

Following on from the success of our 2022 meeting, we are able to confirm the 2023 RCPsych Faculty of Neuropsychiatry annual conference. This will take place on 14-15 September 2023 at our HQ in London. The conference will also be live streamed.

Confirmed Topics

1. Critical issues in brain injury litigation
2. Lord Sir David Ramsbotham lecture
3. Homelessness and Neuropsychiatry
4. Epilepsy cases
5. Neuropsychiatry in children with acute and long covid
6. Managing Aggression in Huntington's Disease
7. Trainee and New Consultants Group

Delegates will also be able to attend workshops on day 1.

Visit rcpsych.ac.uk/events for further details and to register your interest.
Contact: Emma George on:
E: emma.george@rcpsych.ac.uk
T: 0208 618 4143

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UKABIF
The United Kingdom Acquired Brain Injury Forum

TIME FOR CHANGE SUMMIT 2023

Monday 6th November 2023

The Lowry, Pier 8, The Quays, Manchester M50 3AZ

An exciting programme of sessions will include:

- The Acquired Brain Injury Strategy
- Women and Brain Injury
- Experts by Experience Leading the Way
- Supporting Children with Brain Injuries in School

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www.ukabif.org.uk/summit2023

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Brain/Mind Interface: Clinical & Medicolegal Challenges

Thursday, October 5, Royal College of Physicians, 11 Saint Andrews Place, London NW1 4LE

Agenda

Registration: 8.30-9.15

- Welcome. *Dr Mike Dilley, Brain & Mind Ltd, Prof Mark Edwards, Brain & Mind Ltd*
- Healthcare & social drivers to bias and inequality for Brain/Mind Interface. *Dr Ndidi Boakye, The Psych Practice*
- Functional Neurological Disorder: Less Equal than Others. *Prof Jon Stone, University of Edinburgh*
- Traumatic Brain Injury: Why is it so common in seldom heard from groups? *Dr Mike Dilley, Brain & Mind Ltd*
- Can biomarkers decrease inequalities in neuropsychiatric conditions? *Dr Tom Pollak, King's College London & Brain & Mind Ltd*
- Medicolegal Debate. *Leigh Day*
- The Clinical Psychology Practice. The impact of biases & health inequalities through a chronic pain lens; implications for assessment and treatment in clinical practice and medicolegal settings. *Dr Hannah Bashforth, The Clinical Psychology Practice*
- Making the Unequal, Equal – Solutions to Inequalities in Interface Disorders. *Prof Mark Edwards, Brain & Mind Ltd*

Finish: 17.15

"All illnesses are equal, but some illnesses are more equal than others." A day of understanding challenges at the brain/mind interface.

Find out more and book at bit.ly/3Y5mX7L

Cost: £199 CPD accreditation applied for

This event is sponsored by Leigh Day & HCA

BRAIN & MIND

UKABIF Annual Conference

Conference details: 7 November, 2022, Lowry Hotel, Manchester, UK. ***Report by:*** Louise Blakeborough, Healthcare Communications Consultant.
Conflict of interest: None declared.

The United Kingdom Acquired Brain Injury Forum (UKABIF) Annual Summit headed North in November last year. Delegates were welcomed by Amanda Swain, UKABIF Vice-Chair to the Lowry Hotel, Manchester, UK. Collaboration was a key theme with emphasis on working together to deliver patient-centred care and support for people with Acquired Brain Injury (ABI).

Delegates were eager to hear a progress update on the Government's cross-departmental ABI strategy, a key recommendation in the All-Party Parliamentary Group on ABI report 'Acquired Brain Injury and Neurorehabilitation – Time for Change' published in 2018. Eleanor Parry, Head of Long-Term Conditions and End of Life Care Policy at the Department for Health and Social Care, Lead for the ABI Strategy and Chris Bryant, Member of Parliament and Co-chair of the ABI Strategy Programme Board presented a 'status report'. The strategy content is being informed by a recent Call for Evidence (CfE) and Eleanor said: "Using the insight gathered we have built a meaningful structure for the strategy." The strategy development is overseen by a dedicated Programme Board comprising senior officials from relevant government departments to ensure it addresses the wide range of issues that affect the lives of those living with an ABI. Chris commented: "Eleanor is making sure that the Board is getting everything on the page. ABI is a passion of mine and I want a strategy document with deliverable outcomes and a timetable that we can take forward."

The Community Rehabilitation Best Practice Standards from the Community Rehabilitation Alliance (CRA) were discussed by James Crichton-Smith, Strategic Communications Manager at the Chartered Society of Physiotherapy. Published in October, the 60-page document provides recommendations to guide the development, delivery and monitoring of high-quality patient-centred rehabilitation. James said: "These standards present a multiprofessional approach to community rehabilitation with an evidence-based solution that shows what good rehabilitation looks like".

Describing the neurorehabilitation services network development in Great Manchester since 1998 Dr Krystyna Walton, Consultant in Neurorehabilitation, Clinical Director for Neurorehabilitation and Major Trauma Rehabilitation, Northern Care Alliance, and Lead for Greater Manchester Major Trauma Rehabilitation said: "We now provide an effective and efficient neurorehabilitation service that relies on collaboration and delivers for patients, but it's been a challenging and long journey". Dr Jenny Thomas, Consultant in

Rehabilitation Medicine, Rookwood Hospital, Cardiff, UK agreed that the development of Major Trauma Centres has made a positive difference in discussions about neurorehabilitation services and said: "In Wales neurorehabilitation got a seat at the table in the pandemic and now we're ensuring it is embedded into services with teams collaborating across the network."

Significant shortcomings in social work practice, education, and training in the UK were discussed by Dr Mark Holloway, Brain Injury Case Manager and Expert Witness HeadFirst. He presented a review of safeguarding adults with ABI that provides recommendations for social work practice and highlights the need for significant improvements in pre- and post-qualification training and supervision of social workers. Mark said: "ABI knowledge is lacking amongst the statutory services and as a consequence it is not integrated into assessments. Understanding brain injury is crucial otherwise we are failing these people."

There is also a great deal of work required to improve the management of people with ABI in the Criminal Justice System (CJS), but progress is being made. Dr Stephanie Gibb, Neurodiversity Policy Lead, Ministry of Justice discussed the Neurodiversity Action Plan submitted in June following a call for evidence (CfE) on adult neurodiversity in the CJS. Stephanie said: "We're making great strides with a whole system approach to making a difference." She also announced that there will be a Neurodiversity Support Manager in every prison by end of 2025.

As 'gatekeepers' the police have an important role in the CJ process and need to identify and support the needs of individuals with an ABI in custody suites. Gemma Buckland, Policy Adviser for the Criminal Justice Acquired Brain Injury Interest Group and Project Manager for UKABIF's Barrow Cadbury Project and Karene Taylor, Researcher for the Barrow Cadbury Project presented research highlighting the lack of knowledge and understanding of ABI in police custody suites and a lack of screening. This was illustrated by Jordan Ball; an accident on a motorbike left him with a severe brain injury. His father David explained that Jordan is articulate but hides the hidden traumas and complexities of his everyday life. During lockdown Jordan was arrested following driving offences and David said: "The police were accommodating of the brain injury, but the probation service was not understanding at all".

Dr Czarina Kirk, Consultant Neuropsychiatrist Secure Services at Lancashire Care NHS Foundation Trust, Dr Shahzad Alikhan, Consultant Psychiatrist, St Andrews Hospital and Dr Neel Halder, Clinical Director, Elysium Health Care Group presented their secure services network, commissioned in 2021, that provides brain injury rehabilitation. There are 80 secure beds for adults with ABI but none for women. All three speakers emphasised person-centred care and working together to 'improve functional behaviour and reduce dysfunctional behaviour'.

Deputyships can be challenging and the importance of getting it right from the start was discussed by Amy Chater, Partner and Professional Deputy, Leigh Day Solicitors and Dr Shabnam Berry-Khan, Clinical Psychologist and Case Manager, PsychWorks Associates, with emphasis on working collaboratively and managing client and family expectations.

Amanda Swain closed the meeting and thanked the speakers, key sponsors Elysium Neurological, Cygnet Health Care, Irwin Mitchell and Leigh Day and exhibitors. She concluded: "We are making great strides in raising awareness of the issues, changing service delivery and improving overall care. Continue collaborating together and we will make a difference."

The 2023 UKABIF Summit will take place on Monday 6th November 2023 with a pre-conference dinner on Sunday 5th November. www.UKABIFSummit23.org.uk

For information about UKABIF please visit: https://ukabif.org.uk

9th Hull BASH National Meeting On Headache Disorders

Conference details: 28 January,2023. Hull University Teaching Hospital, Hull, UK. ***Report by:*** Fayyaz Ahmed, Consultant Neurologist and Honorary Professor in Clinical Neurology at Hull University Teaching Hospitals NHS Trust and Hull York Medical School, UK. ***Conflict of interest:*** None declared.

The British Association for the Study of Headache (BASH) in collaboration with the International Headache Society (IHS) and the Department of Neurology, Hull University Teaching Hospitals, UK, organised this prestigious educational event on headache disorders in January 2023 at Lazaat hotel and restaurant in Cottingham. The event has been a regular occurrence every other year in Hull since 2005 and is the biggest headache meeting in the UK. The three days of educational lectures for healthcare professionals was followed by a public day in collaboration with the Migraine Trust.

The educational programme covered all aspects of headache disorders from pre-clinical research to evidence based treatment. More than 40 headache specialists from all over the UK delivered lectures attended by 330 delegates including general practitioners, general physicians, neurologists, trainees and allied healthcare professionals. The meeting commenced with a dedicated session for headache specialist nurses and covered evidence based treatments on migraine, injectable treatment and lifestyle support for headache sufferers.

The main event started with the first Vicky Quarshie memorial lecture by the President of the IHS, Professor Cristina Tassorelli from University of Pavia, Italy on medication overuse headaches. Vicky Quarshie was a headache specialist nurse in Hull and a member of the BASH council for many years who died at a young age of 47. Professor Peter Goadsby and Phil Holland spoke about preclinical research on cluster headache and migraine respectively. Dr Farooq Maniyar summarised functional MR imaging in understanding a migraine brain; how it shows activation in the premonitory phase long before the aura and headache phase of migraine attack.

The clinical talks on the first day included a presentation by Dr Shazia Afridi highlighting why it is three times more common in women and how migraines are managed during pregnancy and lactation. The dilemma on who to scan was covered by an entertaining presentation from Dr Giles Elrington. Alex Nesbitt presented up to date research on how sleep and headache disorders are closely linked. The afternoon session was on migraine treatment given by Dr Jane Anderson with special emphasis on managing status migrainosus and Dr Mark Weatherall on preventive treatment options. Professor Manjit Matharu spoke on the trigeminal autonomic Cephalalgia with an excellent summary on how to differentiate between the various subtypes. The difficulties in differentiating trigeminal neuralgia with SUNCT and SUNA and tips on how to manage them was the talk by Dr Giorgio Lambru.

The second day commenced with enlightening lectures on how CSF pressure changes can cause migraine-like headaches. Idiopathic Intracranial Hypertension, common in young fertile females often present with visual symptoms and papilloedema that requires urgent imaging. Professor Alex Sinclair highlighted the latest research and new therapeutic agents in their management. Not every visual symptom is indicative of migraine and Professor Susie Mollan pointed out those that require an ophthalmologist review. Dr Sarah Miller gave an overview on low pressure headaches, how often they are missed and the challenge a neurologist faces in its management as many anaesthetists are still unconvinced on the benefits of a blood patch.

Finding the cause of a secondary headache is as difficult as finding a needle in a haystack, however, they can be life threatening and require careful clinical evaluation in patients presenting with recent onset headaches. Dr Anish Bahra, an advocate of evidence based medicine, discussed some important tips and tricks in identifying and managing them. The morning session ended with a summary of how a general practitioner copes with a 10-minute consultation in primary care. Dr David Kernick, a GPwSI in headache for decades, provided some useful tips to GPs on how to identify and screen a headache presentation. Medication overuse is more common than one thinks and the availability of codeine-based over the counter medication makes it challenging when it comes to patient education, Dr Atwal emphasised. With the increasing elderly population, one sees a growing number of refractory headaches in this age group that have multiple co-morbidities and other prescribed medication on their scripts which makes it difficult to choose a suitable headache prophylaxis. Dr Krishna Dani highlighted these problems with a specific presentation on how migraine and stroke are interlinked, particularly when it comes to aura without headache and increased risk of stroke in those with aura. The session ended with a presentation by Dr Nirmalathan on the new integrated care system (ICS); how this will affect the delivery of headache services in the UK.

The last decades saw the arrival of new migraine-specific therapies targeting the CGRP molecule. Four such biologics are available, all recommended by NICE. Three decades of research by Professor Goadsby and Professor Larsen was behind their development, highlighted Dr Jan Hoffman. He gave an overview on what new therapies are in the pipeline particularly Pituitary Adenyl Cyclase Activating Polypeptides (PACAP). There have been recent advances in some invasive therapeutic options such as occipital nerve stimulation, deep brain stimulation in those with refractory chronic migraine and cluster headaches. Though not widely available and restricted to the very resistant cases, they may have a future prospect in management, said Dr Sarah Miller. The last session covered headaches in children and adolescents with a comprehensive presentation by Dr Ishaq Abu Arafeh. The choice of drugs and new therapeutic options is not straightforward in this age group considering clinical trials are restricted to those above 18.

The conference dinner on the first evening attended by 110 delegates was an opportunity for networking and to gain practical tips from the leading UK experts in headache medicine. As this was the first face to face event following the COVID-19 pandemic, it was welcomed by everyone and the feedback was extremely positive. The meeting offered 15 external CME credits by the Royal College of Physicians, was free to attend and included refreshments and buffet lunch on both days. It was supported through an unrestricted educational grant by Abbvie.

UK Stroke Forum 2022

Conference details: 29 November - 1 December, 2022. ACC, Liverpool, UK. ***Report by:*** Lorraine Azam, non-medical Consultant in the Stroke service at the Royal Preston Hospital, UK. ***Conflict of interest:*** None declared.

The UKSF 2022 conference returned as an in-person conference at the ACC in Liverpool. The three-day conference is the UK's largest multidisciplinary stroke conference with 2022 having record abstract submissions. This report is a snapshot of some of the sessions.

The first day had a well subscribed session on state-of-the-art secondary prevention. Dr Alan Cameron (University of Glasgow) presented how we select patients for cardiac monitoring and what might be the optimal duration to improve detection of atrial fibrillation (AF) after stroke and transient ischaemic attack (TIA). Studies advise we should monitor for longer, which is challenging in the NHS, we therefore need to target the monitoring, perhaps using biomarkers and rule out those who are unlikely to have AF. The PRECISE study will develop a prognostic model using biomarkers and the Cardiac Monitoring Study EOI will look at duration.

Professor Andrew Ross Naylor (University Hospitals of Leicester, UK) asked what stroke physicians need to know about carotid arterial disease surgical management and the new guidelines. He advised to intervene within 14 days and that carotid endarterectomy (CEA) is preferable to stenting, but we still don't know the optimal timing of intervention as more data is needed. Dual antiplatelet therapy (DAPT) for 21 days is recommended in these patients but there needs to be discussion between stroke physicians and vascular surgeons about the role of DAPT after CEA.

Professor David Werring (UCL, UK) looked at the dilemma of when to start anticoagulation after ischaemic stroke caused by AF when the current data does not cover the early stages after stroke – how do we balance risk of stroke versus risk of intracranial haemorrhage (ICH)? There is no clear consensus on timing in the guidelines and we need more data on severe strokes and infarct size; OPTIMAS may tell us more, but early oral anticoagulants (DOACs) look promising.

Dr Gargi Banerjee (UCL) reviewed cerebral amyloid angiopathy and new emerging research in the area. Boston 2.0 now expands the clinical presentation, reducing the age range to 50 alongside a change in the imaging criteria. Iatrogenic CAA was discussed with ever growing case reports for this rare condition.

The second day opened with standing room only in the medico-legal aspects of stroke care with Dr Neil Baldwin (Winfield Hospital, UK) giving an insight into this complex area with case examples. He highlighted that stroke is blessed with a large amount of guidance to support decisions and emphasised the need for clear documentation recording the risks and benefits of care given.

The Princess Margaret memorial lecture was given by Professor Tom Robinson (University of Leicester, UK) recapping the research: To treat or not to treat acute stroke hypertension – is it still an important question? With ICH he advised we need careful lowering particularly over the 1st hour and need to sustain it and reduce variability. With large vessel occlusion, intense blood pressure lowering may increase the risk of ischaemia. The take home message was to restart the oral antihypertensives as soon as able instead of continued use of IV agents.

The second day closed with an interactive and informative session providing a practical approach to assessing the front door patient with vertigo given by Dr Diego Kaski (University College London) exploring how to differentiate between peripheral and central causes to help differentiate between the strokes and the mimics. He gave a practical demonstration of the HINTS+ assessment and the Semont manoeuvre to treat benign positional vertigo (BBPV) but warned to watch out for possible AICA territory strokes as they mimic vestibular issues.

The final day opened looking at stroke in older adults, is it all about age or is it about frailty? Dr Agarwal (Addenbrookes Hospital, UK) noted that age was the most significant factor in ischaemic stroke and early death in the first week after ICH is more likely in older adults. Age should not be a contraindication for thrombectomy as older adults still benefit from intervention, but frailer adults had poorer outcomes.

Dr Jonathan Hewitt, (Cardiff University, UK), looked at multi-morbidity – 50% of those over 65 have two or more conditions and many of these conditions cluster; the more conditions, the worse the outcome after stroke.

Dr Terry Quinn (University of Glasgow, UK) focused on delirium after stroke, only 7% is hyperactive with the rest hypoactive. It is common and will affect at least 1 in 4 strokes and up to half of patients with ICH. Delirium impacts upon rehab engagement and has a legacy effect with functional decline, 5x risk of mortality and higher risk of institutionalisation. Use the 4AT to screen as it has sensitivity and specificity of 0.9 and consider screening twice daily with those at high risk, particularly within the first 24-72 hours. Prevent delirium with basic clinical care, avoid sedatives and use MDT care to treat it.

The closing plenary, what's hot and what's next, gave a taster of future stroke innovation. Among the talks, Dr Graham McClelland (North East Ambulance service, UK) looked at the changing face of pre-hospital care and how it might impact on patient selection and taking treatments into the community to the patient. Rachael Jones (national stroke nursing forum, UK) presented on how non-medical staff from the MDT can impact on new ways of working to enhance TIA diagnostics, investigations and secondary prevention, which was in keeping with other speakers who discussed the use of ACPs, non-medical consultants and physician associates as part of the stroke workforce.

This is a brief insight into some of the talks from a packed multi-disciplinary agenda, more to come this year in Birmingham from the 4th of December 2023.

Report on 15th European Conference on Tourette Syndrome

Conference details: 7-9 June 2023. The Royal Museum for Central Africa in Brussels, Belgium. ***Report by:*** Seonaid Anderson, Chartered Research Psychologist and freelance Neurodiversity Consultant. ***Conflict of interest:*** None declared.

The European Society for the Study of Tourette Syndrome (ESSTS) conference took place 7-9th June at the Royal Museum for Central Africa in Brussels, Belgium. This was the first time it was held in Belgium with assistance from local organisers www.neuro-diverse.org and www.iktic.be.

Doctors, researchers, scientists and numerous patient associations from different nations took part with 150 attendees from 20 countries present. The conference organisers were delighted by the record-breaking attendance with attendees from Australia, Canada, Iceland, Sweden, Norway, Germany, France, Italy, Greece and the Netherlands to name a few.

Another record broken was the number of abstract submissions this year as well as endorsements of the conference by the International Parkinson and Movement Disorder Society (MDS) and the International Association for Child and Adolescent Psychiatry and Allied Professions (IACAPAP). The conference was also graced with the presence of the wonderful Professor Mary Robertson with us on her birthday, the 7th of June – also marked as Tourette Syndrome awareness day!

A meeting of the patient association umbrella called Tics and Tourette Across the Globe (TTAG) also took place as part of the conference event. The support associations discussed collaboration between doctors and patient associations to help support the creation of new associations in countries where none exists.

Although somewhat lacking in participation from Belgian healthcare professionals, the conference was opened with a video message from Hilde Crevits; a Belgian politician from Flanders and member of the Christian Democratic and Flemish party who is currently the Flemish minister of Economy, Innovation, Work, Social Economy and Agriculture.

Amazing add-ons to the conference included a 'training school' for clinicians (physicians, psychologists, psychotherapists, nurses, medical students and other professionals) and behavioural therapy for tics training workshops in French and English to cater for as many Belgian healthcare professionals as possible – www.essts.org

There was also patient participation as a British company presented a new technology that seems to be able to significantly reduce tics with brain stimulation via a wristband.

It feels like in Belgium we are very far behind in terms of awareness of Tourette Syndrome and tic disorders including their diagnosis and treatment. So this conference will leave a legacy for years to come which hopefully will highlight the advances that could be made to improve the lives of those with Tourette syndrome in Belgium as well as those around the world.

Queen Square Multidisciplinary Neuro-oncology Teaching Course

The need for multidisciplinary working in Neuro-oncology is well established but a common theme that will be addressed is the need for better understanding between core specialties within the Neuro-oncology Multidisciplinary Team. To address this, this course has been designed for Trainees, Consultants and Clinical Nurse Specialists in the core specialities of neuro-oncology – Neurology, Neurosurgery, Clinical Oncology, Neuroradiology, Neuropathology and Palliative Care.

Course fees:

Category	Full course rate	Day rate
Consultants	140	100
Trainees	90	70
Students	15	10
UCLH Staff	0	0
Allied professionals (physios, nurses etc)	70	50

E: m.khanom@ucl.ac.uk

To book: www.ucl.ac.uk/ion/queen-square-multidisciplinary-neuro-oncology-teaching-course

27th September 2023: Principles of Neuro-oncology
6th March 2024: Benign and Malignant Tumours
Location: 33 Queen Square lecture theatre
Course Director: Dr Jeremy Rees

The 4th Queen Square Movement Disorders Short Course

The course is designed for neurologists, neurology trainees, and movement disorders enthusiasts from other neuroscience specialties, from the UK, Europe and worldwide. The course is interactive to allow active participation and enhance learning. On completion the participants should be able to manage patients with movement disorders in their clinical practice with updated knowledge and confidence.

The teaching sessions cover all aspects of movement disorders including Parkinson's disease and atypical parkinsonism, tremor, dystonia, tics and functional movement disorders. There are ample opportunities for hands on experience with dedicated workshops on Deep Brain stimulation and Botulinum toxin injections and non-pharmacological management of Parkinson's.

Course fees:

Consultant & Associate Specialists	£350.00
PhD Clinical Trainees & Research Fellows	£200.00
UCL Medical Students, BSc, MSc students	£100.00
Nursing Staff, therapists, paramedics (NHS)	£100.00
Day registration (one day only)	£200.00

Linda Taib: l.taib@ucl.ac.uk

12th-13th October 2023
Location: 33 Queen Square Lecture Theatre, London, UK
Course Organisers: Prof Anthony Schapira and Dr Amit Batla

Stroke One Day Course: Advanced Stroke Neuroimaging

This short course will give an overview of using neuroimaging and mechanical thrombectomy to treat people who have had a stroke. This course will outline methods of quantifying the impact of the stroke using advanced imaging techniques– from penumbral and core infarct size through to methods of imaging recovery from stroke. It will also cover the more familiar aspects of imaging stroke such as using CT and MRI based modalities to evaluate infarcts and haemorrhages.

Speakers: Prof David Werring; Dr David Doig, Dr Richard Perry, Dr Robert Simister, Dr Paul Bentley Dr Sumanjit Gill

By the end of this course you should be able to:

- Select the appropriate imaging modality to evaluate a stroke case
- Understand the ways in which imaging is developing and will be used in the future
- Evaluate the current evidence for endovascular treatment and common complications of this treatment
- Select patients for endovascular treatment
- Use imaging to look for the aetiology of stroke
- Use imaging to differentiate between stroke and stroke mimics

Attendee are invited to submit a case for presentation on the day for discussion with the panel and the audience. Please contact s.gill@ucl.ac.uk for any further information; usual length of presentation being 5-10mins with a 10-15 minute discussion facilitated by the teaching faculty.

The course is accredited with 6 Federation of the Royal Colleges of Physicians of the United Kingdom (RCP) CPD points and you will also receive a certificate of attendance.

Book at bit.ly/3rU7GdO **Fee: £140 for in person**

1st November 2023, 9am - 5pm

Location: Basement lecture theatre, 33 Queen Square, London, WC1N 3AR

Queen Square Multiple Sclerosis (MS) Course

The Queen Square MS Centre team have designed this two-day course as an update, accessible to both specialists and non-specialists (including trainees, GPs and allied healthcare professionals).

10 CPD approved credits applied for.

bit.ly/3OHJswt
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2nd and 3rd November 2023

Location: 33 Queen Square lecture theatre, London [plus online observer registration option]

Course Directors: Professor Ahmed Toosy and Dr Declan Chard

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