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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

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Todd Hardy, Co-Editor.

The ACNR editorial board has been refreshed and our latest issue is filled with a range of excellent articles that reflect the changes.

We begin with Catherine Doogan and Alex Leff from London who review the aims of cognitive rehabilitation, fleshing out the importance of social cognition and metacognition as both an influence and an endpoint in therapy. They implore that cognitive rehabilitation following an acquired brain injury not just be reserved for the period immediately following the injury but be revisited throughout a patient's life.

Alexander Gordon, Daniel Lashley, and Stuart Weatherby from Plymouth argue that headache could be better treated in the NHS by adopting the 2019 BASH guidelines and implementing them into a new headache management system to ensure more patients are treated in a standardised and evidence-based manner.

Riona Mc Ardle, Silvia Del Din and Alison Yarnall from Newcastle tackle the topic of how gait analysis may be able to identify the early gait "signatures" of the different dementias and look ahead to how wearable technologies might be used in the clinic to diagnose and monitor these patients.

Ethnicity and MS is the topic of a review by Ben Jacobs and Ruth Dobson from London. The article brings attention to MS being a disease that affects patients from many different racial backgrounds and ponders what this might tell us about MS disease susceptibility.

In our current series on nutrition and neurological conditions, Christina Englezou and Di Liang from Birmingham offer a primer on subacute combined degeneration of the spinal cord due to vitamin B12 deficiency furnished with illustrative cases.

Vijay Chandran and Donald Grosset from Glasgow tackle the latest on disease modifying therapies for Parkinson's disease.

Our first neurosurgical article is authored by Holly Roy from Plymouth together with co-authors from across the UK, Bangladesh and South Africa and covers how the neurosurgical approach to CNS tuberculosis can be enhanced by multinational collaboration. Our second neurosurgical article comes from Samuel Jeffery in Plymouth and deals with the latest in the diagnosis and management of IIH.

JMS Pearce from Hull provides an historical perspective on the clinical anatomy and disorders of the cervical sympathetic chain. Nikhil Agarwal and Pragnesh Bhatt from Aberdeen write an historical vignette on US neurosurgeon, George Smith, who pioneered cervical anterior discectomy and fusion. Andrew Larner from Liverpool writes on "migralepsy".

Our conference report is from Brendan Sargent reviewing the Liverpool neurological infectious diseases 2021 conference. Rhys Davies reviews a special ACNR podcast of Sri Kodali interviewing ACNR founding editor, Roger Barker and ACNR publisher, Rachael Hansford about the early days of ACNR interspersed with digressions of life in general. ACNR Co-Editor, Ann Donnelly, interviews Guy Leschziner from London about his book on the neuroscience of sleep.

We hope you enjoy this edition of ACNR.

Todd Hardy, Co-Editor
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Fintepla is currently under NICE evaluation.

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Prescribing information can be found on the opposite page

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Rethinking damaged cognition: an expert opinion on cognitive rehabilitation

Catherine Doogan, PgDipNeuropsych, DClinPsych, MPsycSc, HDipPsych, BEd,
is a Clinical Psychologist who has been working in the field of neuro-rehabilitation for the last ten years. She has a specialist interest in generating novel therapeutic approaches to help people with cognitive impairments caused by stroke or Dementia. Through her NIHR funded post-doc work at UCL, she has co-created three digital neuro-interventions; one for people with post-stroke aphasia, one for people with proper-name anomia and dementia. She has also co-designed an immersive virtual reality stimulation paradigm for people with acute, post-stroke neglect. She has a particular interest in how patients and carers experience being involved in co-design and the variety of expectations and experiences they have of participating in neurorehabilitation-based research.

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Abstract
Cognition is frequently damaged by acquired brain injury (ABI). Impaired thinking is both a symptom in its own right and also a barrier to recovery by impacting the patient's insight and awareness and their engagement with rehabilitation. Here we consider the aims, mechanisms and contexts when the goal is to improve cognitive function in patients with ABI.

Cognitive rehabilitation and assessment of function

Cognitive rehabilitation involves the restoration of function in people who have experienced a change in their cognitive abilities. This is usually a return to participation in meaningful activities and improved quality of life. For the purposes of this short review, we will focus on those with cognitive under-functioning caused by acquired brain injury (ABI). Skilled assessment is essential if we want to quantify change, but it is fraught. In a sense, all cognitive tests are proxies of what they claim to measure and there is no standard battery that will adequately characterise all patients. Data from 'off-line' pen-and-paper tests, if possible, should be complimented with more practical assessments in function. Finally, as cognitive impairments are almost always relative, one needs to establish a reasonable estimation of a person's pre-morbid function.

Mechanisms

It is helpful to think about this using the analogy of motor recovery. There are two key aspects: the first relates to what we are trying to change, the second to how we might change it.

What are we trying to achieve?

When looking at outcomes in the motor recovery literature, there is a clear distinction between restitution and compensation [1]. In the former, the manner of the repaired behaviour (e.g. drinking from a cup) is indistinguishable from the pre ABI state (the drinking movements are carried out in the same way as they were pre injury); in the latter, the same goal is achieved but the way that the task is completed is visibly different from before. Here, compensatory strategies are employed, i.e. new ways of doing old things. The gold standard for motor recovery is restitution rather than compensation, with some arguing that compensatory strategies should be discouraged as they limit the final ceiling of observable recovery [2]. Does this paradigm hold true for cognition? It is hard to tell as the measurable output (a given behaviour) can be produced by many different combinations of internal states and thought processes that themselves are hard to quantify (e.g. indistinguishable reading performance across subjects, can be driven by several very different patterns of cortical network activity [3]). Indeed, it is our view that almost all cognitive rehabilitation relies on some form of strategy-based process. For example, a major cause of frustration in supporting memory function in a patient going back to work may involve introducing them to what they believe to be novel and thus more effortful approaches, such as note taking, reminders and fatigue management. However, these explicit strategies are simply drawn from the common armoury of mental methods used in everyday functioning. Indeed, the patient will have used a different range of these to carry out tasks previously, but they will have become so ingrained as to feel effortless. The process of this type of rehabilitation is to facilitate patients to develop behaviours that they initially might resent, as it represents loss of their previous identity; yet with practice and habituation, these behaviours become implicit.

The behaviours that we are trying to change either relate to how patients interact with others (e.g. communication, social cognition, vocational rehabilitation) or how they view themselves (e.g. insight and awareness). The goal is to help the patient navigate toward these altered, recovering cognitive states, and maintain them.

How are we trying to achieve it?

In motor recovery, the general principle is mass practice with feedback, so the patient undergoes many hundreds or thousands of guided repetitions to reach their goal. Is the same true for cognition? Interventions targeting behaviour change generally do not follow a massed-practice approach, rather they require the patient to migrate from one behavioural state to another. This can occur, rarely, with a single event (one-shot) or single-session learning [4], but more often requires a series of tailored interventions which incrementally bridge the gap between the current state and desired goals. When helping a patient adjust their behaviour and/or world view, new problems may

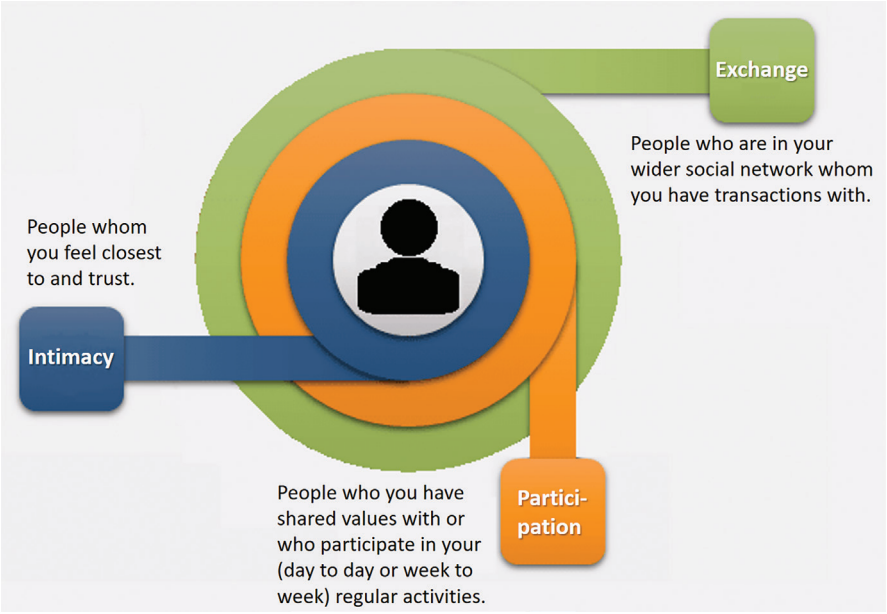

Figure 1 above: Diagram of three main tiers of social relationships that most people have. These are disrupted by brain injury of any kind in the majority of cases. The labels not only describe the depth of these tiers but also avenues for therapists to intervene. Intimacy: these are the relationships that offer the most support to the person, but also often come under the most strain post ABI. Participation: relationships that are sustained by regular contact such as at work or friendship groups. Exchange: often acquaintances, these people, whilst sparsely connected, still enrich the person's life.

Figure 2 below:
In cognitive rehabilitation, both the person's representations of their relationships with others (social cognition) and their ability to mentalise their own thought processes (metacognition) are potential therapeutic targets.

arise. For example, it is not uncommon for patients to experience a deterioration in their mood as therapists work on insight and awareness relating to the impact of their ABI and what this means for them. Therefore, psychological well-being needs to be assessed and treated throughout the patient pathway [5].

Techniques and approaches to improving patients' cognitive functioning are legion but can be conceptualised along the following two key dimensions of complexity and social context (visualised with the individual at the centre and concentric rings representing carers and loved ones, then wider social contacts such as friends and colleagues). Simpler interventions include psychoeducation, which can be aimed at the person with ABI, their family or other people they interact with (e.g. helping work colleagues support the patient). Moving through the social contexts, more complex interventions include: 1) for the individual with ABI: increasing insight and awareness (see metacognition section below), working on individual cognitive impairments, adjustment and acceptance [6]; 2) for carers and loved ones: conversation partner training, couples or family therapy; 3) wider social contacts such as the workplace: facilitating communication, coaching, negotiating reasonable adjustments [7].

Social context and social cognition

We all exist in a complex web of social relationships which both define our sense of place in the world and help us understand who we are. Social cognition has been defined as any cognitive process that involves other people either at a group level or on a one-to-one basis. ABI can have a devastating effect on social cognition which enables these meaningful interactions with others. Cognitive impairments and the effect brain injury has directly and indirectly on mood affect these relationships, often putting them under intolerable strain [8]. Patients with brain injury find maintaining friendships difficult and harder still to acquire new ones, social webs can become eroded and therefore the responsibility of social support can fall on an ever reducing number of people. Positive outcomes for rehabilitation are closely linked to this support and interventions, therefore, need to be systemic and encompass the patient's key relationships, which can include psychoeducation; however, the needs of the carer are often overlooked. This can be addressed by providing psychotherapeutic interventions that take account of the loss that they have suffered and their adjusted role(s). We have found that a group setting where relatives gather in a real or virtual 'carers' café' to share their lived-experiences with each other and a Clinical Psychologist [9] can be powerful and authenticating.

Metacognition

Metacognition refers to the ability to reflect on, monitor and control other cognitive processes, often in the absence of feedback. In the most reductive form, behavioural therapies can be used to improve how people

with ABI respond without requiring them to understand much about why their behaviour has changed. But for most of what takes place in cognitive rehabilitation, patients need to be able to mentalise themselves. Metacognition refers to this ability, to reflect on, monitor and control one's own cognitive processes. Metacognitive impairments are very common after ABI, and like social cognition, are rarely formally assessed, perhaps because there is no agreement on which tools are best to do this [10]. Therapists often talk about patients' readiness to change being associated with better outcomes - metacognitive awareness is part of this and supports learning in the undamaged brain [11]. Increasing self-awareness in patients with ABI encourages them to form a perspective of themselves outside of themselves. Methods to achieve this include sensitive sharing of assessment results, guided reflection using video recordings of the patient, supervised feedback from others (e.g. family members and/or work colleagues). Holistic interventions have also shown promise in improving ABI patients' metacognitive abilities [12]. Shifts in self-awareness and subsequent consistent changes in behaviour often take time to be established. The implication of this is that the optimum timing of intensive rehabilitation may be distal to the brain injury. This necessitates that health care systems monitor and reassess patients with ABI throughout their lifespan.

Key take home points:

- Before intervening we need to understand who the patient is. Holistic assessment using multiple methods of testing are necessary to establish this.
- The patient's conceptualisation of their relationships (social cognition) and how they view their own cognitive processes (metacognition) are both necessary targets for rehabilitation.
- Therapeutic strategies must involve: i) working with people in the patient's social network; ii) building insight and awareness; iii) the time window for interventions should never close.

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The New National Headache Management System: an easy solution to provide more efficient and evidence-based headache services

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Headaches make up 30% of all Neurology outpatient consultations [1]. There is distinct variability in the management of headaches by Neurologists, leading to unnecessary disparities in the standard of care and likelihood of response between patients. A significant proportion of patients with headache diagnoses do not receive the evidence-based treatments recommended in national or international guidelines [2], and substantial numbers of patients are not receiving preventive therapies [3]. Ziegeler et al. found that a third of patients reporting to a tertiary headache centre had not received preventive therapy in line with guidelines, and half had never been prescribed a preventive treatment [2]. Considering that 46% of the global adult population are estimated to have a headache disorder [4], this lack of a consistent, evidence-based approach is somewhat incongruent with the patient socio-economic impact.

It is probable that lack of adherence to current headache guidelines is a multi-faceted issue. This variation in treatment (and therefore patient outcome), although unexplored [2], is not likely to be a simple educational issue. To add to this, an educational approach, in the form of seminars and workshops, does not have entirely positive evidence to support its use in implementing changes to patient care [5]. It seems more probable that there are also structural issues within the health service that in some way preclude patients with headache disorders from gaining appropriate care. For example, using only doctors to care for patients with such a common condition may cause bottle-necking in access, and may not be an appropriate use of clinical resource. The current context of a global pandemic has shown us the importance of using the skillsets of all NHS staff working together for patient care. For headache care this could involve greater use of nursing colleagues or allied health professionals such as Pharmacists.

To facilitate such an aim, an easily used and standardised approach is essential. We believe that the guidelines from the British Association for the Study of Headache (BASH) [6], could facilitate such an approach.

BASH Guidelines and the New Headache Management System

BASH published their latest guideline on the management of headache in 2019. The intent is to assist the clinician when seeing a patient in real time, and help allied health professionals in managing patients using a simple and standardised menu of care. The guideline is user friendly and logically structured, initially discussing the diagnostic process and how any clinician may recognise features of different primary headache disorders on initial presentation, as well as red flags and the role of imaging in a succinct fashion that can be easily communicated with patients. It then provides brief summaries of the principles and treatment options in migraine, medication-overuse headache, tension-type headache, and the trigeminal autonomic cephalalgias.

All treatments recommended in the guideline have been consistently shown to be effective by good quality randomised placebo controlled trials, and are not included unless they have been considered to consistently have class A evidence and have been recommended in two or more of the NICE, SIGN, AHS, or EFNS guidelines. It has received accreditation from the Royal Pharmaceutical Society, and national patient charities such as The Migraine Trust.

To further facilitate use of the 2019 guidelines, a national headache management system has also been developed (headache.org.uk).

The system can support allied health professionals in managing primary headache disorders in line with the latest BASH guidance. The tool can be simply accessed via headache.org.uk and will allow more effective facilitation of patient self-management.

After accessing the website, the tool is easy to navigate as both a patient and healthcare professional, with a flow chart type process to take both parties directly to their required information (Figures 1 and 2).

This avoids having to navigate a large amount of preamble beforehand, as is so often the case with guidelines. The included patient information area contains a number of downloadable patient information sheets that contain information consistent with the guidance in the section provided for healthcare professionals, as well

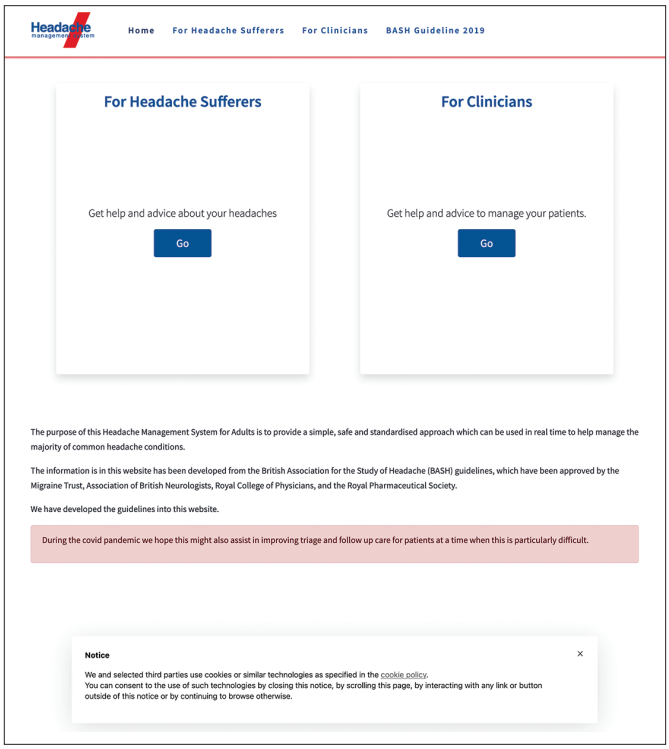

Figure 1. The headache.org.uk homepage.

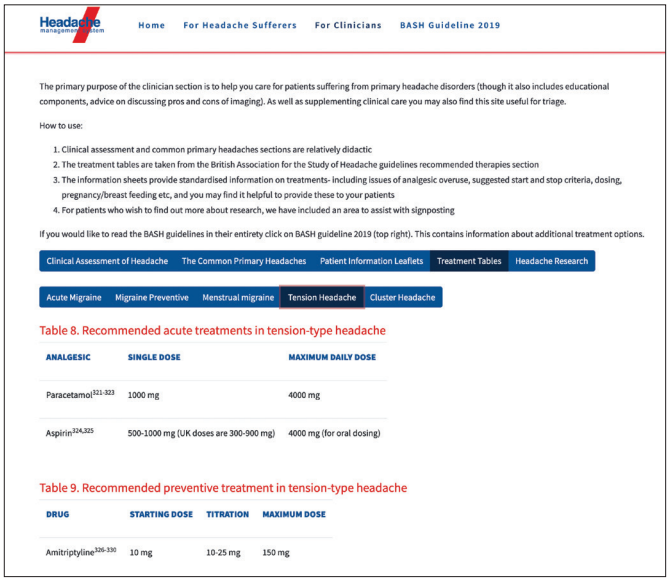

Figure 2. An example of the functionality of the management system when one searches for treatment options for tension headache.

as additional information on self-care strategies. An example of one such information sheet is shown in Figure 3.

Utilising this system will allow more consistent messaging between healthcare professionals. The use of patient information sheets and educational videos further allows a multimodal approach to patient information such that this can be tailored to individual communication need. Its readability means it could also be used as a learning tool for healthcare students to ensure people are trained to practice in line with the evidence base.

We envisage this having multiple benefits. Consistent messaging will improve adherence by reducing confusion for patients provided by conflicting information, and patients will have confidence that their ongoing self-care is being conducted in an evidence-based fashion. Adoption of a more systematic approach on a national level by a range of healthcare professionals across primary and secondary care settings will hopefully allow greater parity of care for patients, improving the statistics on inequitable treatment previously mentioned.

Figure 3. An extract from the migraine preventive treatment patient information leaflet provided through the "For Headache Sufferers" part of the management tool

As the shape of training changes are introduced, with diversion of Neurology Trainees towards dual training in General Medicine and Neurology, it is inevitable that the result will be reduced experience in neurological conditions compared to their counterparts in the training model currently extant. It is possible that a more systematic approach to headache care will also be of assistance in this regard.

This system could also assist busy Neurology departments from a service provision perspective by making triage for patients with primary headache conditions more easily standardised and efficient.

Therefore, we are advocating for the integration of a headache management system into current services as a supplement to the usual process of care. This could help provide evidence-based care in a more efficient fashion, and also provide a more adaptable approach to service provision made requisite by the ongoing pandemic and incoming shape of training changes.

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Gait analysis as a clinical tool for dementia: current perspectives and future challenges

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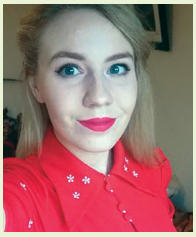

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Abstract
Gait, the way that we walk, requires complex cognitive functions. Gait may be a useful early marker for dementia diagnosis, as gait impairments precede and reflect cognitive decline. Early diagnosis of dementia enables individuals and their families to make informed decisions about their care plans, and allows researchers to understand preclinical and prodromal disease stages, providing novel targets for drug therapies. As such, a range of biomarkers are being developed to improve early and accurate diagnosis, including gait analysis. This editorial will outline how gait analysis can support the clinical diagnosis of dementia, including evidence of unique signatures of gait which can aid the identification of cognitive impairment and discrete dementia disease subtypes, the potential use of wearable technology to assess gait in the clinic and the real world, and key recommendations for the future implementation of gait into the diagnostic toolkit for dementia.

Prevalence of dementia is rapidly rising, with an estimated 131 million people worldwide expected to be diagnosed with the condition by 2050 [1]. Dementia is characterised by multiple progressive cognitive impairments which impair an individual's functional abilities [2]. There is currently no cure, but both pharmacological and non-pharmacological therapies may be effective at treating key symptoms.

Developing methods for earlier and more accurate diagnosis is a research priority [3]. This allows researchers to better understand the disease in early and predementia stages, providing novel targets for drug therapies. It also allows people with dementia and their families to make timely decisions surrounding their disease management, power of attorney and future care plans. There are a range of novel biomarkers being developed to improve the way we diagnose dementia, such as cerebrospinal fluid and blood markers, and neuroimaging correlates [4]. However, many of these options are costly and invasive, and may not be feasible to employ wide-scale.

Inexpensive and non-invasive screening tools which detect subtle disease-related markers are required to support clinical decision-making. The advent of wearable technology, ambient sensors and smartphone applications have led to the development of digital biomarkers, which collect data relating to everyday functions, such as gait and sleep patterns, physical and social activity, and cognitive functions [5,6]. This may prove a fruitful endeavour to support dementia diagnosis.

How can gait analysis support clinical diagnosis of dementia?

Gait refers to the manner in which a person walks. Gait analysis is gaining significant interest as a digital biomarker [7-10]. Although gait appears automatic, it actually relies on significant cognitive processes [11]. Gait impairments may be considered a red flag for cognitive decline and neurodegeneration, with a significant slowing of gait speed preceding dementia diagnosis by up to fourteen years [12].

Gait can be assessed within clinical settings through clinical examination, motor rating scales and self-report subjective scales such as the Tinetti Performance-Orientated Mobility Assessment or the Berg Balance Scale. These are commonly applied and useful for detecting change over time, but are limited by subjective variations and difficulty in identifying subtle gait impairments, which may not be observable to the human eye [13]. Simply measuring gait speed can provide a more objective and sensitive assessment, but is not specific enough to characterise different diseases or subtypes of the same disease. However, there is more to gait analysis than assessing gait speed; there is a rich range of gait characteristics that can be examined [14], and which provide useful information regarding cognitive impairment, disease progression and efficacy of therapeutics in a variety of neurological

conditions [15]. Traditional gait assessment methods, such as instrumented walkways, commonly record spatiotemporal gait characteristics, such as those relating to pace (e.g. gait speed, step length), variability (i.e. changes in spatiotemporal characteristics of gait, such as how much step length changes across steps), rhythm (i.e. temporal characteristics of gait, such as step time), asymmetry (i.e. differences between left and right steps) and postural control (i.e. characteristics that contribute to keeping individuals upright while walking). These characteristics provide a more holistic picture of gait, allowing us to identify unique signatures of gait in dementia. For example, a systematic review reported that people with dementia take shorter step lengths and demonstrate greater variability compared to older adults without dementia [16].

Gait analysis may also be an effective differential marker of dementia disease subtype [7]. Recent findings reported that people with Lewy body disease demonstrated a more variable and asymmetric gait compared to Alzheimer's disease, suggesting Lewy body disease has a unique signature of gait that may reflect their underlying discrete pathology [17,18]. There have also been different gait patterns reported between Alzheimer's disease and "non-Alzheimer's dementias", suggesting gait may be useful as a differential marker for subtypes such as vascular or frontotemporal dementia [19,20]. These subtypes of dementia may have similarities in clinical presentation and underlying pathology and thus be difficult to distinguish initially, leading to inaccurate diagnosis and inappropriate disease management [21]. Inexpensive tools to support differential diagnosis of dementia subtype are required both clinically and in research to ensure the accurate characterisation of patients' or participants' disease subtype to ensure they are treating or researching the correct pathological targets [4]. Additionally, accurate characterisation of disease subtype in early stages can support research into the identification of putative disease-modifying therapies.

How can clinicians measure gait in people with dementia?

Traditional gait analysis

Much of the evidence surrounding gait's potential as an early and differential marker of dementia and its subtypes are derived from traditional gait assessments, such as instrumented walkways [18]. This proves a barrier to uptake of quantitative gait assessment in clinic, as traditional gait analysis techniques require dedicated space, specially-trained staff and significant time to set up [9]. However, wearable technology may provide a solution to inexpensively and easily assess gait in the constrained space of the clinic, with several algorithms validated to analyse gait in clinical settings [22].

Wearable technology for gait analysis

Wearable technology comprises of singular or multiple sensors (e.g. accelerometers – a device that senses motion and velocity, inertial measurement units – a device with multiple types of sensors which measures the position or orientation, force and angular rate of the body) which can be attached to the body or embedded within clothing or accessories, and which capture information and measurements relating to individual's function, such as gait. Due to their inexpensive nature, they have garnered significant interest for clinical applications such as their utility as diagnostic tools for Parkinson's disease [23]. With the call for digital biomarkers to support dementia diagnosis [24], wearable-based gait analysis may be a feasible tool to aid the clinician's toolbox.

Using wearable technology to assess gait in people with dementia has been shown to be feasible in both traditional laboratory settings and within the real world [25]. People with dementia and prodromal stages of dementia have demonstrated significantly impaired gait patterns when assessed with wearable technology in the lab, such as slower gait, shorter steps, longer times to complete a step and greater gait variability [26-28]. One study has even demonstrated the efficacy of wearable-derived signatures of gait for differentiating dementia disease subtypes, with moderate-to-good accuracy for distinguishing dementia with Lewy bodies from Alzheimer's disease, and good accuracy for differentiating Parkinson's disease dementia from Alzheimer's disease [29]. This supports the proposal that wearable-based gait assessment may be a supportive tool for identifying cognitive impairment and differentiating dementia subtypes.

Analysing gait in the real world: potential for clinical use?

However, gait assessment in a lab or clinic only provides a snapshot of an individual's gait performance, generally showcasing their best possible performance. Because of wearable technology's ability to be worn continuously for prolonged time periods [13], we can now acquire a more realistic picture of an individual's true gait performance, such as how they move and adapt to varying environments [30]. There is significant interest regarding the use of wearable-based real-world gait analysis to monitor and detect neurological conditions [13,23,31,32]. Pilot studies have demonstrated that real-world gait impairments demonstrate good discriminatory accuracy to differentiate people with dementia from healthy older adults [33]. However, lab-based gait assessment may be better at distinguishing between dementia subtypes, as differences in signatures of gait impairment are only found in very short ambulatory bouts in the real-world [34]. Further work is required to explore the efficacy of real-world gait assessments for differential diagnosis of dementia. Additionally, there are a number of limitations to real-world gait which need to be addressed before implementing such assessments into clinical practice. These include the lack of consensus on which metrics best describe gait in the real-world (e.g. spatiotemporal or frequency based metrics), and the need for further validation of algorithms for detecting gait in the real-world as most have been developed for lab-based controlled environments [34]. In light of the COVID-19 pandemic, it is clear that developing digital tools, such as wearable technology and its outcomes, is vital for healthcare services, given the necessity of remote clinical practice and diagnostic assessments [35].

What steps need to be taken to use gait as a diagnostic marker for dementia?

Digital biomarkers and assessment tools are not yet validated for clinical practice, and there are a number of steps that must be taken before they will be implemented for widespread clinical use. In line with Rochester's [35] roadmap for the development and implementation of digital outcomes, such as those produced via wearable-based gait assessment, we propose the following suggestions for researchers, clinicians and regulatory bodies to consider.

Firstly, we need to move beyond small pilot studies to maximise our data and understanding of how best to assess gait in the real world. Collaborative efforts are required to synthesise and standardise current gait assessment protocols, data processing and digital mobility outcomes [35]. Research should incorporate the voices of clinicians, scientists, patients and regulatory bodies to ensure that the information produced by wearable-based gait analysis is relevant and improves clinical decision-making beyond what can be achieved through careful neurological examinations [36].

Secondly, wearable-based algorithms for gait analysis have been designed for controlled indoor settings, and do not account for changes in the environment that are frequently experienced in the real world (e.g. moving around a cramped room compared to walking outside) [37]. This makes interpretation of gait impairments difficult, as we cannot identify which gait impairments are due to disease or due to the environment an individual is walking within [38]. Criterion validity should be demonstrated by comparing digital outcomes to gold-standard references (such as traditional gait assessment) in both the lab and real-world, and assessing the feasibility, acceptability and usability of wearable technology with both clinicians and people with dementia. Similarly, construct validity should be demonstrated through longitudinal studies that assess how digital outcomes reflect more traditional measures of disease, such as cognitive and functional assessments [39].

Third, efforts to validate wearable-based algorithms and digital outcomes for identifying dementia, differentiating dementia subtypes and monitoring disease progression should be submitted to relevant regulatory bodies (e.g. European Medicines Agency) for approval.

Finally, cost-effectiveness of using wearable technology as a diagnostic tool must be assessed and demonstrated. Of particular importance here, quick and easy-to-use pipelines for processing and interpreting digital

outcomes must be developed with the intention to implement widely. As an ideal example, the busy clinician would upload the data to a platform which would quickly process the outcomes and provide information regarding how likely the patient is to have a specific dementia subtype based on their gait patterns.

Conclusion

To summarise, we can see that gait assessment may be a useful way to identify cognitive impairment and distinguish dementia subtypes. With advances in wearable technology, it is easier to assess gait in the clinic and the real-world, which may be informative and supportive to the diagnostic process, thus serving as a digital biomarker. However, further work is required to validate wearable-based gait assessment as a diagnostic tool for dementia, including recruitment to larger collaborative studies, improved algorithm development, standardised protocols and digital mobility outcomes, and inclusion of patients, healthcare professionals and regulatory bodies in the research pathway. With the validation of wearable technology, we open up a myriad of possibilities, including more accurate diagnosis and monitoring of disease progression, increased confidence in stratification for clinical trials, and the ability to continuously and remotely assess responses to drug therapies or behavioural interventions, improving the potential for person-focused tailored care.

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Ethnicity and multiple sclerosis – moving beyond preconceptions

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Abstract
Historically, Multiple Sclerosis (MS) was thought to be substantially more common in individuals from European ancestral backgrounds. Recent studies have challenged this preconception, with a concerning increase in incidence among Black British and African American individuals. In this review we provide a brief overview of the evidence for ethnic variation in MS risk, summarise potential explanations for this variation, and illustrate how these observations could be used to provide potential insights into disease biology.

Multiple Sclerosis (MS) is a complex autoimmune disease of the Central Nervous System (CNS) that affects ~0.1% of the population and is a leading cause of disability in young people. The pathogenesis of MS is thought to involve an interplay between genetic factors – of which the MHC type II allele HLA DRB1*15:01 is the most potent – and environmental risk factors such as smoking, early life obesity, Infectious Mononucleosis (IM), and low serum vitamin D [1]. Historically, MS was thought to be substantially more common among individuals of European ancestry than in individuals from other ethnic groups and ancestral backgrounds. This view is being challenged by more recent studies demonstrating a concerning increase in the incidence of MS among Black British and African American individuals. Here we provide a brief overview of the evidence for ethnic variation in MS risk, summarise potential explanations for this variation, and illustrate how these observations could be used to provide potential insights into disease biology. It is worth emphasising upfront that there is an important distinction between 'ethnicity' – a subjective label which incorporates an individual's national, cultural, religious, and physical identity – and 'ancestry', a more objective term which describes the origins of the genetic variants inherited by an individual. Both ancestry and ethnicity are correlated to an extent with genetic risk factors and the environmental milieu to which an individual is exposed. As all individuals carry genetic material derived from different ancestral populations, attempting to characterise an individual's ethnic background is intrinsically an oversimplification. This oversimplification is worth bearing in mind when considering large-scale epidemiological studies in MS, which typically focus on reported ethnicity rather than genetically-determined ancestry.

Prevalence of MS in minority ethnic populations

Several cross-sectional observational studies have reported a higher prevalence of MS in individuals of Northern European ancestry. This observation appears robust both when comparing prevalence between countries, and when comparing ethnic groups within the same country [2,3]. The Global Burden Of Disease study reported the highest age-standardised prevalence of MS in Northern America (164.6/100,000) and Western Europe (127.0/100,000), with the lowest rates seen in Sub-saharan Africa and Oceania (<5/100,000) [4]. A large cross-sectional study of individuals of White, Black, and South Asian ethnicity in the UK found adjusted prevalence rates of 180/100,000, 74/100,000, and 29/100,000, respectively.[2]

Prevalence estimates reflect both the rate at which new diagnoses are made (incidence) and the mortality rate. Differences in disease prevalence between groups could therefore be due to differences in incidence or in mortality – either directly related to the disease process, or at a wider population level. Additionally, relatively small changes in disease incidence take time to impact on prevalence, and remain influenced by population mortality. The lower reported prevalence of MS in people from minority ethnic backgrounds could be explained by either lower incidence or higher mortality in this population subgroup, or may result from a combination of the two. Bias in diagnosis leading to later diagnosis and/or falsely lowered incidence may also impact on population prevalence. There is evidence that mortality is higher in individuals with MS from Black British/African American ethnic backgrounds under the age of 55 [5], and cognitive biases have the potential to impact both the time to diagnosis and the absolute number of diagnoses in minority ethnic populations. Prevalence and incidence estimates for MS are also confounded by both access to diagnostic facilities (e.g. MRI scanners) and data quality, and these factors make it difficult to draw strong conclusions for some parts of the world, including Sub-saharan Africa, Latin America, and much of Asia [4].

Incidence of MS in minority ethnic populations

Recent incidence data have challenged the historic view that MS is predominantly a disease affecting White individuals. Data from the cohort of US military veterans serving in the Gulf war period (1990-2010s) reported that MS incidence in this cohort was higher among individuals of African

American ethnicity (12.1/100,000 person-years) compared to White individuals (9.3/100,000 person-years) [6]. Various potential explanations for this observation have been postulated: military personnel are predominantly male, are exposed to a peculiar mix of environmental exposures which may increase the risk of MS non-uniformly across ethnic groups (e.g. close contact with others which may facilitate transmission of EBV, irregular shiftwork, noxious chemicals, intense physical labour etc), may be subject to increased medical attention, better health insurance plans, and may be more likely to seek medical help with subtle weakness/incoordination due to high physical conditioning, all of which may introduce a diagnostic bias. Furthermore, this is a young cohort, and it is possible that individuals from different ethnic groups are more likely to manifest with, or be diagnosed with MS at different ages. Recent data from our group in East London demonstrate that the odds of MS are greater among Black British individuals than White British individuals below the age of 30 [7]. The observation of higher MS incidence in minority ethnic individuals has also been made in the Kaiser Permanente Cohort from the USA, which reported incidence rates of 10.2/100,000, 6.9/100,000, 2.9/100,000, and 1.4/100,000 for Black, White, Hispanic, and Asian individuals respectively [8]. Generally, these data suggest that the incidence of MS among people of African ancestry living in the USA and UK may be equal to, if not higher than, individuals of European ancestry.

Mechanisms of ethnic variation in MS risk

'Ethnicity', as recorded and measured in observational studies, is variously presented as a composite measure of self-identified social grouping along lines of national, ancestral, or cultural tradition. It is an intrinsically vague concept, especially when based on self-report, which serves as a noisy proxy measure that an individual may share certain genetic and environmental risk factors with a certain group. The advent of biobank-scale datasets which collect genotyping/sequencing data and detailed phenotypic data, such as the UK Biobank, permits a genetically-based definition of ancestry, often defined by genetic principal components, to complement data on self-reported ethnicity.

Explanations for ethnic variation in MS risk can be broadly divided into hypotheses about why there might be real variation in genetic and environmental risk factors between ethnic groups, and hypotheses about why this observation may be an artefact. Clearly, disparities between ethnic groups in terms of healthcare access and language proficiency, and unconscious (or conscious) diagnostic biases on the part of treating clinicians may bias towards lower MS incidence in minority ethnic populations. This is a particularly pertinent consideration in countries such as the US where access to healthcare is highly correlated with ethnicity, and minority ethnic groups are less likely to have health insurance coverage [9].

Various biological reasons may explain ethnic disparities in MS incidence. Ethnic variation may be a proxy for geographical variation. There is a well-established latitudinal gradient in MS incidence and prevalence, with MS incidence increasing as latitude increases. This gradient can be observed both between and within countries, and so could feasibly either explain or be explained by ethnic differences in MS incidence as people from different ethnic groups are non-randomly spread across a country. Latitude may itself may be a proxy for either environmental variables (e.g. vitamin D, sun exposure, UV light, pollution, affluence, EBV infection), or genetic factors (i.e. MS susceptibility alleles which vary in frequency between populations).

Geographical location cannot entirely account for the association between ethnicity and MS. Migration studies have highlighted that geographical location prior to adolescence is the key determinant of MS risk, with first generation migrants assuming the MS risk of their new homes if they migrated before adolescence, but retaining the MS risk of their countries of origin if they migrated in adulthood [10]. It appears that second generation immigrants to "high risk" countries such as Denmark have an MS risk that is significantly higher than their parents, and potentially even higher than that of the country to which they have migrated [10]. Second, even in fully 'admixed' populations, in which people from different ethnicities live in roughly the same areas for roughly the same period of time, MS incidence rates still appear to differ, suggesting that geography alone cannot explain the variation [2,3].

It is feasible that certain behaviours or environmental risk factors associated with MS risk, such as smoking, may be more or less common in certain groups. Additionally, it may not be possible to overcome residual confounding by factors which may influence MS risk such as household crowding and socio-economic status which may explain subtle differences between individuals living in geographically similar areas. In fact, some environmental factors may interact with ethnicity, in that their effect on MS risk may either be potentiated or blunted in certain ethnic groups, as we have recently suggested for Infectious Mononucleosis and smoking based on data from an East London GP cohort [7]. Third, it has been suggested that higher MS incidence among Black individuals in some studies may be explained by lower vitamin D levels, however this has not been borne out by the empirical data [11,12].

Despite mounting epidemiological evidence that MS incidence in individuals of Black ethnicity may be as high, if not higher, compared to White individuals, genetic studies of MS have focused on individuals of European ancestry [13-15]. The few studies which have examined genetic determinants of MS susceptibility in individuals of non-European ancestry have recapitulated the strongest association signal in Europeans at the Major Histocompatibility Complex (MHC) locus. These studies have not yet discovered novel loci but have broadly supported the view that the direction and magnitude of genetic effects does not differ substantially between populations for many established MS risk variants, with a couple of intriguing exceptions [16-18]. Understanding the genetic architecture of MS susceptibility in non-European groups – particularly individuals of African ancestry – will improve our understanding of the causes of MS in all individuals, may lead to identification of new drug targets, and may help pave the way for personalised diagnosis, prognosis, and treatment of MS.

Concluding remarks

Contemporary epidemiological data have overturned the historical notion that MS is predominantly a disease of White individuals. Clinicians should be aware of the increase in MS incidence among individuals of non-European ancestry, specifically among people with African ancestry and ensure they do not fall prey to the misconception that a diagnosis of MS is less likely if an individual is not in a "traditionally" high-risk group. Studying MS in ancestrally diverse populations can help to expand our understanding of disease biology, particularly with respect to the role of, and interactions between, genetic and environmental risk factors. Importantly, including individuals of all ancestries in MS research ensures that advances in diagnosis and management of MS are equitably shared by all persons with MS regardless of ethnic background.

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Idiopathic Intracranial Hypertension: a review of diagnosis and management

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Abbreviations
IIH – Idiopathic Intracranial Hypertension
CSF – Cerebrospinal fluid
OCT – Optical Coherence Tomography
IIHWOP – Idiopathic Intracranial Hypertension Without Papilloedema
ICP – Intracranial Pressure
BMI – Body Mass Index
LPS – Lumboperitoneal shunt
VPS – Ventriculoperitoneal shunt
ONFS – Optic Nerve Sheath Fenestration
VSS – Venous Sinus Stenting
VF – Visual Fields
VA – Visual Acuity
HA – Headache

Abstract
With the increasing prevalence of obesity, the incidence of idiopathic intracranial hypertension (IIH) is rising. Headache and threat to vision are the predominant features and the principal cause of morbidity and reduced quality of life. Identification of papilloedema must prompt urgent investigation to exclude any underlying cause and management should be multi-disciplinary, focusing on protecting vision and reducing headache burden. Weight loss is the most effective and only disease modifying treatment for IIH but surgical interventions may need to be considered in some patients. Whilst optic nerve sheath fenestration and CSF diversion have established roles in protecting vision, there is increasing interest in venous sinus stenting and bariatric surgery as additional interventions that may have efficacy in the treatment of this condition.

Idiopathic Intracranial Hypertension (IIH) is a disorder of uncertain cause, characterised by raised intracranial pressure in the absence of hydrocephalus or a mass lesion. It typically affects obese women of childbearing age and although a self-limiting condition in the majority of patients, it can be the cause of significant psychological morbidity. Previously known as Benign Intracranial Hypertension, this misnomer failed to recognise the small proportion of patients who develop irreversible, life-changing visual loss, the prevention of which should be the primary concern of those involved in the diagnosis and treatment of the condition. The management of IIH requires a multidisciplinary approach with specialist input from neurology, ophthalmology, dietetics, radiology and neurosurgery. Patients with IIH will present via primary care and acute hospital services, and therefore a broad understanding of the condition is essential for both General Practitioners and Emergency Physicians. The purpose of this review is to summarise the diagnostic and management challenges and to highlight best practice guidelines as well as current trends and controversies.

Epidemiology

The incidence of IIH varies around the world and is related to the prevalence of obesity in the general population. The estimated global incidence is 0.14 per 100,000 per year in populations with an obesity prevalence of <10% but rises to 1.48 per 100,000 per year in populations where the prevalence of obesity is >20% [1]. Recent large studies from the UK further highlight the relationship of both obesity and deprivation with IIH. In Wales, where obesity prevalence has increased from 29% in 2003 to 40% in 2017, the prevalence of IIH has increased six-fold to 76 per 100,000 and the incidence three-fold to 7.8 per 100,000 per year. This peaks at 180 per 100,000 and 23.5 per 100,000 per year in obese women [2]. A similar trend is found in England [3,4]. More than 80% of patients are female and 85% are under 45 years old at diagnosis (mean 28-30 years) [1-3]. In men, the mean age at diagnosis is slightly higher (32-33 years) but the proportion of cases diagnosed in childhood is also higher (approximately 30% of male cases, 10% of female cases). Social deprivation, even after adjusting for obesity, has an association with IIH, with fewer cases identified in the least deprived geographical areas. Interestingly, whilst the association with obesity is seen across both female and male patients, the relationship with deprivation is only a feature of female cases [2,3]. Based on current trends, the cost of treating IIH in English hospitals is projected to be $462million by 2030, nearly a 50-fold increase since 2002 [3].

Diagnostic criteria

Both the modified Dandy [5] and Friedman criteria [6] are widely used in the diagnosis of IIH. A modified version of the Friedman criteria, adopted by a consensus of UK experts [7] offers a pragmatic approach for clinicians (Table 1).

Clinical features and investigations

Headache is the predominant symptom and the major cause of morbidity and reduced quality of life [5,7-9]. The typical raised intracranial pressure headache (positional, early morning, exacerbated by Valsalva manoeuvre) is not universal and studies indicate that migraine (chronic or episodic) is the most common phenotype [8]. Headache of IIH may coexist with chronic daily headache, medication over-use headache and migraine and is frequently associated with other symptoms including photophobia, phonophobia, visual obscurations and diplopia (with or without abducens palsy). Pulsatile tinnitus (thought to be caused by turbulent flow in the intracranial venous system) is also commonly reported, as is neck, back and radicular pain (Table 2) [9].

Table 1: Diagnostic criteria for IIH

Modified Dandy Criteria [5]

1. Signs and symptoms of increased intracranial pressure
2. Absence of localising findings on neurologic examination
3. Absence of deformity, displacement, or obstruction of the ventricular system and otherwise normal neurodiagnostic studies, except for evidence of increased cerebrospinal fluid pressure (>200 mm water). Abnormal neuroimaging except for empty sella turcica, optic nerve sheath with filled out CSF spaces, and smooth-walled non flow-related venous sinus stenosis or collapse should lead to another diagnosis
4. Awake and alert
5. No other cause of increased intracranial pressure present

Modified Friedman Criteria [6]

1. Required for diagnosis of pseudotumor cerebri syndrome*
   - A. Papilloedema
   - B. Normal neurologic examination except for cranial nerve abnormalities
   - C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
   - D. Normal CSF composition
   - E. Elevated lumbar puncture opening pressure (≥250mmCSF in adults and ≥280mmCSF in children [250mmCSF if the child is not sedated and not obese]) in a properly performed lumbar puncture

A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.

2. Diagnosis of pseudotumor cerebri syndrome without papilloedema
   In the absence of papilloedema, a diagnosis of pseudotumor cerebri syndrome can be made if B–E from above are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy
   In the absence of papilloedema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied, and in addition at least 3 of the following neuroimaging criteria are satisfied:
   - i. Empty sella
   - ii. Flattening of the posterior aspect of the globe
   - iii. Distension of the perioptic subarachnoid space with or without a tortuous optic nerve
   - iv. Transverse venous sinus stenosis

**Pseudotumor cerebri syndrome: synonym for IIH used predominantly in the USA*

UK Consensus Criteria adapted from Friedman Criteria [7]

1. IIH Diagnostic criteria
   - A. Papilloedema
   - B. Normal neurological examination (except sixth cranial nerve palsy)
   - C. Neuroimaging: normal brain parenchyma (no hydrocephalus, mass, structural lesion or meningeal enhancement). Venous sinus thrombosis excluded in all.
   - D. Normal CSF constituents
   - E. Elevated lumbar puncture pressure ≥25cmCSF
2. IIH without Papilloedema (IIHWOP) Diagnostic criteria
   Presence of criteria B-E for IIH plus:
   Unilateral or bilateral sixth cranial nerve palsy
3. Suggestion of possible IIH without Papilloedema (IIHWOP) Diagnostic criteria
   Presence of criteria B-E for IIH plus:
   Three neuroimaging findings suggestive of raised intracranial pressure
   - Empty sella
   - Flattening of posterior aspect of the globe
   - Distension of the peri-optic subarachnoid space ± a tortuous optic nerve
   - Transverse venous sinus stenosis

Table 2: Symptom frequency in IIH adapted from Markey et al [9]

Symptom	Frequency (% of patients)
Headache	75–94%
Nausea with or without vomiting	42–73%
Photophobia, phonophobia, or both	72–75%
Transient visual obscurations	68–72%
Pulsatile tinnitus	52–60%
Back pain	53%
Dizziness	52%
Neck pain	42%
Visual loss or blurring	32%
Cognitive disturbances	20%
Radicular pain	19%
Horizontal diplopia	18%

By definition, papilloedema (optic disc swelling due to raised intracranial pressure) is present and its identification must prompt urgent action to find any treatable cause and protect vision. Initial assessment should include visual acuity, formal visual fields and dilated fundoscopy; early ophthalmology assessment including retinal photography and optical coherence tomography (OCT) is also recommended [7]. OCT provides quantitative, objective measurements of papilloedema which complements clinical assessment particularly as visual fields can be unreliable and non-organic visual loss can coexist [10,11]. It is important not to be falsely reassured by normal visual acuity which can be maintained despite significant loss of the peripheral visual field. Blindness from IIH is rare (0.42-2% [2,3,10] but milder visual impairment is more common. Visual loss may occur at any time, be insidious and asymptomatic so careful monitoring for detection of subclinical visual field loss is essential. The reported incidence of any reduction in visual acuity or field is wide-ranging [9] and the most common field abnormalities are blind spot enlargement, constriction, nasal loss and arcuate defects [12]. A subset of patients who meet all the other criteria for IIH but do not have papilloedema (IIHWOP) is described and these patients do not appear to have a risk to vision [6,7] but should be monitored for the development of papilloedema.

All patients with papilloedema should undergo cranial imaging (MRI with venography or CT with venography) within 24 hours to rule out a mass lesion, hydrocephalus or venous sinus thrombosis before proceeding to lumbar puncture [7]. Lumbar CSF pressure correlates well with intracranial pressure [13] but should be performed in the lateral decubitus position and allowed to settle with the legs extended prior to manometry to avoid an artificially raised pressure. An opening pressure of greater than 25cmH_20 is required to meet the diagnostic criteria although, given diurnal variations in ICP, a single reading should be interpreted with caution when it does not fit the clinical picture [7]. Where doubt exists or lumbar puncture contraindicated (e.g. due to coexisting Chiari malformation), intracranial pressure monitoring can be considered.

Other secondary and potentially reversible causes of raised ICP, including endocrine dysfunction, iron deficiency anaemia and medications (Table 3) should be ruled out, particularly when the patient is not the typical phenotype (non-Caucasian, male or BMI<30Kg/m^2). Associated conditions including sleep apnoea, polycystic ovary syndrome and risk of cardiovascular disease should also be considered [4-7].

Imaging findings

Radiological stigmata are summarised in Table 4 and have high specificity but relatively low sensitivity for IIH, other than transverse sinus stenosis which is both sensitive and specific. However, imaging

Table 3: Associations and secondary causes of raised ICP, adapted from Markey et al. [9] and Mollan et al. [7]	
Secondary causes of raised intracranial pressure	
Iatrogenic	Antibiotics Tetracycline, minocycline, doxycycline, nitrofurantoin, sulphonamides, and nalidixic acid Hormones Levonorgesterel implant, thyroxine, growth hormone, corticosteroids and tamoxifen Vitamin A (including isotretinoin) Other drugs Lithium, ciclosporin, indomethacin, cimetidine
Haematological	Anaemia Polycythaemia vera
Respiratory	Obstructive sleep apnoea Hypercapnia, Chronic Obstructive Pulmonary Disease
Endocrine	Addison's disease Cushing's syndrome Adrenal insufficiency Thyroid & parathyroid dysfunction
Renal	Chronic kidney disease/renal failure
Autoimmune	Systemic Lupus Erythmatosus Sjögren's syndrome
Syndromic	Down Syndrome Craniosynostosis Turner Syndrome
Venous outflow obstruction	Central venous sinus thrombosis Jugular vein thrombosis Superior Vena Cava syndrome

Table 4: MRI signs diagnostic of IIH, adapted from Kwee and Kwee [14]		
MRI Sign	Sensitivity	Specificity
Empty Sella	62.2	90.7
Posterior displacement of pituitary stalk	41.2	84.0
Meningocoeles	9.3	99.2
Posterior globe flattening	56.3	95.3
Optic nerve head protrusion	29.1	97.0
Optic nerve enhancement	13.2	95.9
Optic nerve sheath distension	68.6	86.1
Optic nerve tortuosity	36.9	88.4
Transverse sinus stenosis	84.4	94.9
Slit-like ventricles	14.5	89.9
Tight subarachnoid spaces	6.1	97.1
Inferior position of cerebellar tonsils	19.2	92.8

findings should be correlated with clinical features of IIH as these signs may be present in the absence of raised intracranial pressure. For example, pituitary height and globe configuration may persist after normalisation of ICP and resolution of papilloedema [14] and primary empty sella has been reported in 8-35% of the general population [15].

Medical and non-surgical management

The only disease modifying treatment in typical IIH is weight loss. Up to 15% weight loss may be required to achieve remission so patients should receive support from dietetics and weight management programmes [7]. There is increasing evidence for the role of bariatric surgery, which is discussed below.

Medical therapies are used to protect vision and reduce headache burden. Acetazolamide, a carbonic anhydrase inhibitor that reduces CSF production, is frequently used in an attempt to protect vision but side effects including paraesthesia, fatigue, diarrhoea, alterations in taste (dysgeusia), nausea and vomiting can result in the drug being poorly tolerated. In the IIH Treatment Trial, a double-blind randomised placebo-controlled study, acetazolamide in combination with a low-sodium weight-reduction diet, had a modest effect on visual field function and improved quality of life measures [5] however the evidence to either recommend or reject its use remains insufficient [16]. Other diuretics including furosemide are sometimes used although efficacy remains uncertain [7]. Topiramate, which has some inhibitory effect on carbonic anhydrase, is a mild appetite suppressant and is efficacious in episodic migraine, has a role in some patients [8].

Management of headache can be challenging so involvement of a clinician with experience in headache management is important, particularly as multiple headache phenotypes, particularly migraines, may coexist [7]. Triptans, topiramate, non-steroidal anti-inflammatories, paracetamol, beta-blockers, tricyclic anti-depressants and sodium valproate are amongst the range of therapies used, however high-quality evidence to guide decision making in IIH is lacking [8]. Patient education about the use of analgesia to avoid medication over-use symptoms is essential and opioid medications should be avoided [7].

Whilst most patients will have relief of headache following therapeutic lumbar puncture, the effect is short lived as CSF is rapidly replenished. Serial lumbar puncture, which can lead to chronic back pain, is not recommended for headache although may be used as a temporising measure when there is concern about rapidly progressing visual loss [7].

Surgical management

Surgical interventions are typically reserved for patients with visual loss refractory to medical treatments and include CSF diversion with a ventriculoperitoneal (VPS) or lumboperitoneal shunt (LPS) or with optic nerve sheath fenestration (ONSF). There is increasing evidence regarding the efficacy of endovascular venous sinus stenting (VSS) [17-19] and bariatric surgery [20-22], but these are not currently routine practice for IIH in most centres in the UK. There are no controlled trials comparing any of these interventions in IIH and the reported outcome measures in the literature are very heterogenous, making comparisons problematic [23].

Patients should be referred for urgent CSF diversion or ONSF when vision is imminently threatened (Fulminant IIH) or when there is a significant deterioration in visual function despite optimal medical management. CSF diversion for headache alone is rarely recommended and should only be considered as part of a multidisciplinary approach following a period of intracranial pressure monitoring [7].

Optic nerve sheath fenestration

The exact mechanism by which ONSF relieves papilloedema is not fully understood. It is thought that decompression of the perioptic subarachnoid space allows CSF egress and reaccumulation is prevented through scarring [24]. ONSF is very successful at improving papilloedema (90.5%) and visual fields (65.2%) but has less effect on improving visual acuity (44.1%) and headaches (49.3%). It has a favour-

Table 5: Summary of outcomes of surgical procedures for IIH, adapted from Kalyvas et al [23]. Figures are percentage of patients for each outcome

Procedure (pooled n)	Improved VF %	Improved VA %	Improved HA %	Improved Papilloedema %	Failure Rate %	Severe complications %
ONSF (n=818)	65.2	44.1	49.3	90.5	9.4	2.2
CSF Diversion (n=609)	66.8	55	69.8	78.9	43.4	9.4
VSS (n=825)	72.7	64.6	72.1	87.1	11.3	2.3
Bariatric surgery (n=50)	83.3	100	99.3	100	10.8	29.4

VF Visual Fields, VA Visual Acuity, HA Headache

able safety profile with only 2.2% suffering a severe complication, however a significant proportion (16.9%) go on to have additional interventions such as CSF shunting due to inadequate symptom control [23]. It is only performed in a few centres in the UK but is more widespread elsewhere in the world.

CSF diversion

Shunting is the most frequently performed surgical intervention in IIH, with approximately 8% of patients having a shunt procedure [2,3]. A shunt is a tube that diverts CSF from the ventricle or lumbar subarachnoid space to another body space where it is absorbed into the bloodstream. The shunt contains a valve which controls the amount of fluid passing through the tubing. Most commonly, the distal tube is placed in the abdominal cavity, although the pleural space and right atrium of the heart can also be utilised.

CSF diversion is effective in improving papilloedema (78.9%) visual fields (66.8%) and visual acuity (55%) but shunt failure and complications are high [23]. A lumboperitoneal shunt may appear to be the less invasive option and it does avoid the obligatory temporary disqualification from driving, however due to a lower revision rate, VPS is usually recommended for visual deterioration in IIH [7]. Furthermore, LPS can cause an iatrogenic Chiari malformation. Complications related to both VPS and LPS include infection, shunt obstruction, catheter migration/malposition/disconnection, over-drainage, intracranial haemorrhage, slit ventricle syndrome and abdominal pain [23]. Obese patients are at significantly higher risk of distal catheter migration, where the abdominal catheter coils in the subcutaneous tissue and requires surgical reimplantation [25]. Nearly 10% of patients suffer a severe complication and more than 40% have failure of their shunt. Many patients require multiple shunt operations, with a mean of 2.6 revisions per patient [2,23].

Headaches frequently initially improve following CSF diversion although iatrogenic low-pressure headaches occur in 28% of patients [9]. Programmable valves can be adjusted using an external magnet allowing the opening pressure to be titrated to patient symptoms. The addition of an anti-gravity (which alters the opening pressure according to body position) or anti-siphon (which prevents excessive drainage during postural changes) device can further protect against over-drainage and low-pressure symptoms. A telemetric pressure sensor can be added proximal to the shunt valve to help guide valve programming and provides useful diagnostic data in the assessment of suspected shunt malfunction. Although meta-analysis indicates CSF diversion is effective for the treatment of headaches (Table 5) [23] this may not be sustained and patients can continue to have significant headache morbidity despite a functioning shunt and being in ocular remission. In one series 79% of shunted patients had persistent headaches at 2 years [26], with chronic daily headache, migraine, medication over-use, and low pressure symptoms contributory [7,8]. A third of patients have multiple hospital admissions in the year following diagnosis [3] and unscheduled hospital admissions are twice as high in those who have undergone CSF diversion compared to those who have not [2]. Severe headache is the reason for presentation in 79% [27] and unfamiliarity with the unique challenges of managing IIH can lead to unnecessary imaging and interventions. Current UK consensus guidelines advise against CT, shunt x-ray or lumbar puncture in shunted patients in the absence of papilloedema or suspicion of infection, with a recommendation to focus on evaluating the headache phenotype, eliminating medication over-use aspects and offering appropriate medical therapies [7].

Endovascular venous sinus stenting (VSS)

VSS has emerged as a possible treatment in medically refractory IIH based on the belief that venous outflow obstruction from transverse sinus stenoses is at least partly contributory to its aetiology. This has been contentious however as CSF diversion or removal (with reduction in ICP) has been demonstrated to reverse venous sinus stenosis indicating that stenosis is the result of raised ICP not the cause [9]. There may, in fact, be two distinct types of venous sinus stenoses: extrinsic compression (termed non-venogenic) as a consequence of raised ICP and less commonly, intrinsic focal venous stenosis (venogenic type) typically due to arachnoid granulation hypertrophy, fibrosis or deposition. As it is now widely accepted that venous hypertension and stenosis may play a role in the pathophysiology there is a compelling argument that when surgical intervention is considered necessary, VSS should be considered above ONSF or CSF diversion as it is the only intervention to act directly on venous sinus haemodynamics [28]. Careful patient selection is critical and requires venography, manometry and measurements of pressure gradients across the stenotic sinus to determine suitability for stent placement [18,23]. Outcomes from uncontrolled studies are very favourable in terms of visual function and headache improvements, particularly given the lower complication and failure rate compared to CSF diversion (Table 5) [17,18,23] but selection bias in these studies is likely. Whilst VSS is an important part of the armamentarium in some neurosurgical centres it is not universally available in the UK and high quality evidence is required to further support its use in the treatment of either visual deterioration or headache in IIH [7,28].

Bariatric surgery

There has been much interest in a possible role for bariatric surgery in IIH given that it has been demonstrated to be a successful, cost-effective and safe treatment for severe obesity when conservative strategies fail [21,22]. Meta-analyses [20,21,23] of small uncontrolled studies in IIH have reported significant improvements in BMI, CSF opening pressure, headache and papilloedema however complication rates are high and evidence quality inadequate to draw firm conclusions from. Most recently however, the IIH Weight Trial, a multi-centre parallel-group randomised clinical trial has reported that bariatric surgery is superior to community weight management intervention in lowering intracranial pressure. Importantly this effect, as well as significantly lower weight in the surgery group, is sustained at two years and is associated with improved quality of life measures. Whilst there was no significant difference between the two groups in terms of headache disability or visual function the additional weight loss achieved in the surgery group has a favourable impact on disease remission as well as a wide range of additional health benefits [22].

Conclusions

With the increasing prevalence of obesity, the incidence of IIH will continue to rise presenting both clinical and service provision challenges.

Clinicians should be mindful of the principles of protecting vision and reducing headache burden and awareness of current guidance will facilitate more consistent and evidence-based care. A multidisciplinary approach involving clinicians with experience in managing IIH is required for the diagnosis, surveillance and treatment of this condition and management strategies should focus on disease modification through weight loss. CSF diversion remains the principal surgical treatment to protect vision when non-surgical strategies fail but the long-lasting implications of this in terms of hospital admissions, complications and revision surgery should not be underestimated. There is however increasing evidence for the role of venous sinus stenting and bariatric surgery which may support a wider range of surgical interventions. High quality research is needed to better understand both medical and surgical treatment options with a view to improving visual outcomes, headache morbidity and quality of life.

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Subacute combined degeneration of the spinal cord in functional vitamin B12 deficiency states

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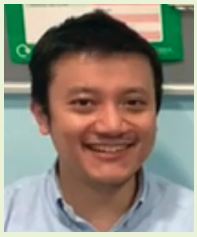

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Abstract

Vitamin B12 is an essential enzymatic cofactor in multiple cellular metabolic pathways. Deficiency states can arise as a result of both depletion of absolute systemic levels and pathological processes that block its ability to act as an enzymatic cofactor. The latter is also known as functional vitamin B12 deficiency. This can cause a variety of systemic, haematological, and neurological manifestations, some of which may be irreversible if not promptly treated. Neurological syndromes include subacute combined degeneration of the cord (SCDC), peripheral, optic, and autonomic neuropathies, and neuropsychiatric or cognitive deficits. This review presents a case series of vitamin B12 deficiencies leading to SCDC, and we include the clinical features, significant investigations, treatments, and prognoses.

Vitamin B12 is the term for a group of structurally similar chemicals called 'cobalamins'. The two most important biological cobalamin forms in humans are methyl-cobalamin and adenosyl-cobalamin. Methylcobalamin is a cofactor for the enzyme methionine synthetase, which converts homocysteine to methionine. Methionine can then be activated to S-adenosylmethionine which is important for myelin lipid synthesis and DNA methylation [1,2]. Adenosylcobalamin is essential for the enzyme L-methylmalonyl-CoA mutase in mitochondria. This converts L-methylmalonyl-CoA to succinyl-CoA, important for the metabolism of amino acids and fatty acids. A schematic diagram of the metabolic pathway is shown in Figure 1. Note that the precursor molecules of methylmalonic acid (MMA) and homocysteine are now available for testing. Their build up is suggestive of metabolic block at the cobalamin utilisation step and could indicate both a quantitative and qualitative deficit.

Most of the human vitamin B12 stores come from dietary sources. Vitamin B12 absorption is complex and is dependent on a series of 'carrier' molecules throughout the digestive system. The process begins in the oral cavity where haptocorrin, also known as R-binders, found in saliva, complexes with vitamin B12. Subsequently in the stomach, gastric parietal cells secrete intrinsic factor which binds to vitamin B12 and help its transport to and absorption from the terminal ileum. Interruptions at any point along this pathway could lead to B12 deficiency (Table 1).

One of the best-studied causes is pernicious anaemia, an immune-mediated process against the gastric parietal cells responsible for producing intrinsic factor (IF). Deficiency due to decreased dietary intake is uncommon in developed nations. However, those with gastrointestinal conditions, dietary restrictions, and/or polypharmacy can be at risk. Some commonly used drugs such as proton pump inhibitors, metformin, contraceptives and hormonal replacement therapies can cause malabsorption of vitamin B12 [3,4,5]. In contrast, functional B12 deficiency is caused by qualitative deficits in its ability to function as enzymatic cofactors. The inhaled anaesthetic agent Nitrous Oxide (N_2O) is one such example. Awareness of N_2O and its neurological complications has increased in recent years due

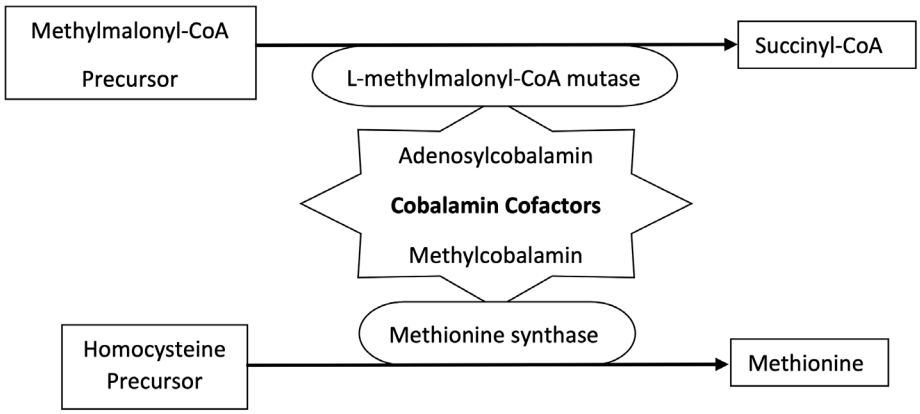

Figure 1. Two forms of cobalamin, adenosylcobalamin and methyl cobalamin play central co-factor roles for the enzymes L-methylmalonyl-CoA mutase and methione synthase respectively. Succinyl -CoA and methionine are critical to cellular functions including DNA methylation, fatty acid and amino acid metabolism, and of particular relevance to the nervous system, myelination of nerve axons. Absolute deficiencies of cobalamin cofactors or interruptions of enzymatic activities of their respective enzymatic activities can lead to increased precursor levels in the form of MMA and homocysteine. Elevated MMA and homocysteine levels can be measured in laboratory tests.

to its use as a recreational drug. N_2O interferes with the action of the central cobalt atom in B12 and inactivates methylcobalamin, thus blocking intracellular enzymic reactions [6,7].

Clinical features: subacute combined degeneration of the cord

Regardless of the mechanism of vitamin B12 deficiency, the neurological system is particularly vulnerable to deficiency states. In fact, a significant proportion of cases seem to present with only neurological syndromes, and available data support the division of neurological and haematological abnormalities [1,2]. One of the most recognised presentations is subacute combined degeneration of the spinal cord (SCDC). Pathologically, SCDC refers to the selective, but combined degeneration of the dorsal column and corticospinal white matter tracts. SCDC typically presents with sensory ataxia, with or without spastic paraparesis or a sensory level [1,6]. Deep tendon reflexes (DTR) can be brisk or diminished [7]. B12 deficiency is thought to lead to demyelination of the dorsal columns, although the causative mechanism is not well understood [9].

Table 1. Causes of B12 deficiency along its metabolic pathway

Metabolic pathway	Causes of deficiency
Dietary intake (animal proteins, supplements)	Malnutrition (alcoholism, eating disorders) Parenteral nutrition Veganism/Vegetarianism
Gastric acid and pancreatic enzymes release B12 from food proteins	Malabsorption (Achlorhydria, atrophic gastritis, gastrectomy/bariatric surgery, drugs, coeliac disease) GI disease (Inflammatory bowel disease, Helicobacter pylori gastritis, parasitic infections, bacterial overgrowth) Pancreatic insufficiency (cystic fibrosis)
B12 binds to HC (stomach)	
Proteases release HC/B12 complex (duodenum)	
B12 attaches to IF, and the B12/IF complex binds to the receptor cubilin to be internalised (terminal ileum)	Pernicious anaemia Mutations in genes responsible for B12 transport/uptake (Imerslund-Grasbeck syndrome)
B12 is detached from IF and binds to TCII (circulation)	
Intracellular uptake of B12/TCII complex via TCII receptor	
Intracellular action of lysosomes free B12 from TCII	
B12 utilised for production of methionine (cytosol) and succinyl-A (mitochondria)	N_2O toxicity

HC, Haptocorrin; GI, Gastrointestinal; IF, Intrinsic factor; TCII, Transcobalamin II; N_2O, Nitrous oxide.

Other neurological complications of vitamin B12 deficiency

Vitamin B12 deficiency can also present with a symmetrical, sensorimotor neuropathy, which is typically axonal. However, cases of demyelinating neuropathy have been reported [11,12], manifesting similarly to Guillain Barré Syndrome (GBS). Overlap syndromes of myeloneuropathy manifesting with absent DTR and extensor Babinski's reflexes are also well recognised.

Optic neuropathy or atrophy has also been reported, but this is less common compared to peripheral neuropathy or myelopathy [1]. Involvement of the autonomic nervous system is possible, usually presenting with urinary/bowel incontinence or erectile dysfunction [8].

Cognitive impairment and neurobehavioral changes have been observed mainly in the elderly. The cognitive decline can be fast, and improvement is expected with replacement therapy [13]. MRI of the brain can reveal subcortical hyperintensities on T2 weighted images, as well as cortical atrophy [13]. However, these findings are not specific to B12 deficiency and co-morbidities of each individual should be taken into consideration.

Diagnosis

There is increasing availability of testing for serum vitamin B12, homocysteine, and methylmalonic acid levels. Serum vitamin B12 levels can provide an indication of absolute body stores. However, a normal B12 level with elevated homocysteine and methylmalonic levels can still be indicative of a functional B12 deficiency with qualitative deficits in vitamin B12 utilisation.

Treatment

Early replacement of vitamin B12 is essential to avoid prolonged neurological symptoms or incomplete recovery. Intramuscular hydroxocobalamin is recommended at a dose of 1mg on alternate days, usually for up to two weeks. In cases of severe neurological disease, the duration of treatment can be prolonged and the BNF suggests continuation of intensive replacement therapy until no further neurological improvement is seen [15]. Maintenance therapy with intramuscular hydroxocobalamin 1mg every 2 months should then be offered.

Oral replacement therapy could be considered in cases of dietary deficiency, however current guidelines support the use of intramuscular replacement in all cases presenting with neurological complications [2,15,16]. In cases of N_2O toxicity, avoidance of further exposure from recreational or medicinal sources is as important as the replacement therapy. Patients with concurrent anaemia can develop hypokalaemia during vitamin B12 treatment and potassium replacement might be needed in such cases [16].

Case 1

A 27-year-old man presented with four weeks of progressive distal paraesthesia affecting both feet and hands. Clinical examination revealed ataxic gait, reduced tone and DTR in the upper limbs but brisk DTR in the lower limbs. Babinski's response was negative. Vibration and joint position senses were reduced at the ankles with intact pain and temperatures sensations, and no sensory level. Power was normal.

On review of the drugs history, he admitted to daily use of N_2O inhalation for recreational purposes over the preceding 6 months.

Investigations revealed low serum B12 at 148ng/L (187-883), with high levels of MMA at 2978nmol/L (0-360), and homocysteine >125µmol/L (6.7-15.2). MRI of the whole spine showed a longitudinally extensive T2 high signal change from the cervico-medullary junction to T10-11 level, affecting the dorsal columns (Figure 2, images A1 and A2).

A diagnosis of SCDC due to B12 deficiency was made based on clinical, laboratory and radiological findings. He was treated with intramuscular injections of hydroxocobalamin 1mg on alternate days for 2 months. At the current time of follow up there have been some improvements in gait but there continues to be distal paraesthesia in all limbs.

Case 2

A 67-year-old man presented with subacute progressive distal paraesthesia in all limbs and decline in mobility. He has a history of gastric adenocarcinoma treated with partial gastrectomy and chemotherapy. Examination revealed an ataxic gait, with normal tone and power. DTR were present in the upper limbs and brisk in the lower limbs, with normal Babinski's reflex. Joint position and vibration senses were reduced to the ankles, with no sensory level and preserved pain and temperature sensations.

B12 was normal at 301ng/L, but there was increased homocysteine (15µmol/L) and MMA (1578nmol/L). MRI of the whole spine showed high T2 signal in the dorsal cervical spinal cord extending from the cervico-medullary junction to C6 level, in keeping with SCDC (Figure 2, image B1).

He was treated with intramuscular injections of hydroxocobalamin 1mg on alternate days for 2 months, with improvement of his mobility from wheelchair bound to walking with a stick.

Case 3

A 27-year-old female with Ehlers Danlos syndrome presented with two-months' history of distal paraesthesia in both hands, followed by paraesthesia ascending from toes to the umbilicus. On review of the history, she had frequent Emergency Department attendances for shoulder dislocation requiring reduction at least weekly in the last year. On each occasion

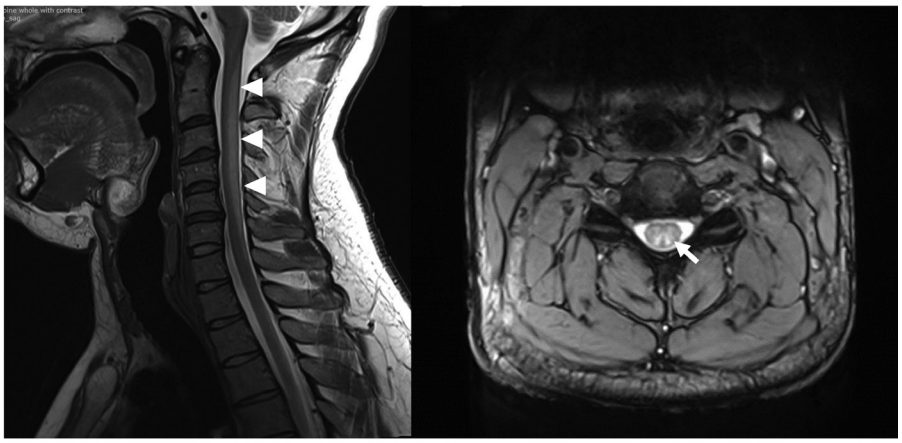

Image A1 *Image A2*

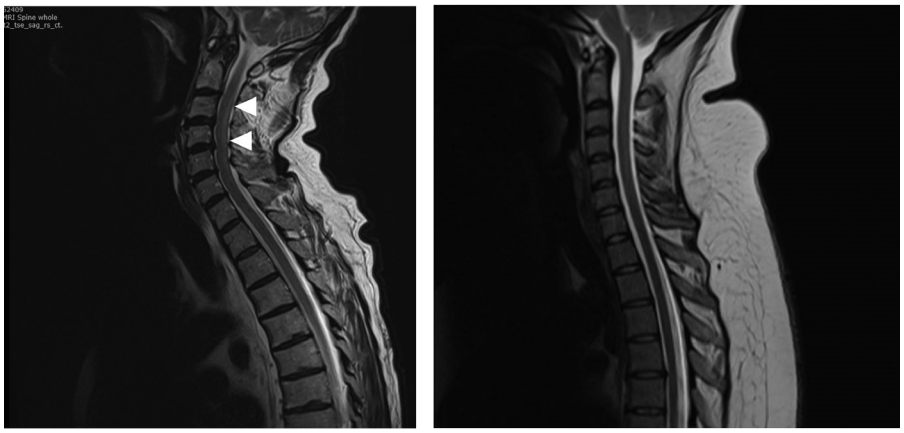

Image B1 *Image C1*

Figure 2. MRI Spinal Imaging findings in B12 deficiency related SCDC.
Case 1, Image A1: SCDC has a typical radiological appearance of a longitudinal segment of increased signal on T2-weighted images, usually extending from the cervical to the thoracic cord (arrowheads). Contrast enhancement is not usually found [6,7].
Case 1, Image A2: Axial T2 images show increased signal in the posterior columns, known as the "inverted V sign" (arrow) [6,9].
Case 2, Image B1: similar dorsal column T2 signal changes extending from cervico-medullary junction to C6 (arrowheads).
Case 3, Image C1: relatively unremarkable appearing T2 weighted imaging of cervical spine in case of biochemically confirmed functional B12 deficiency.

she used Entonox (50% N_2O, 50% oxygen) as an inhalational analgesic for up to 30 minutes.

Examination revealed sensory ataxia, a sensory level to T8, reduced vibration and joint position sense to the ankles, DTR brisk at ankles, and positive Babinski's reflex bilaterally. Tone and power were normal.

MRI of the whole spine was unremarkable (Figure 2, image C1) and the B12 level was actually elevated at >2000. However, plasma MMA was significantly elevated at 2722nmol/L, as well as homocysteine at 31µmol/L. Functional B12 deficiency was diagnosed based on history, examination and laboratory findings. She was treated with intramuscular hydroxocobalamin 1mg on alternate days for two weeks. Follow up is pending.

Key learning points

1. Case 1 demonstrated that SCDC often has a typical radiological appearance of a longitudinal segment of increased signal on T2-weighted images, usually extending from the cervical to the thoracic cord (Figure 2 images A1, B1). Contrast enhancement is not common [6,7]. Axial T2 images show increased signal in the posterior columns, known as the 'inverted V sign' (Figure 2, image A2) [6,9].
2. However, the extent and severity of MRI changes are not indicative of disease severity [10]. Case 3 also demonstrated that some cases of SCDC can have normal MR imaging (Figure 2, image C1). In cases where there is negative imaging investigation, but the clinical suspicion remains strong for SCDC then biochemical tests should be performed.
3. Cases 2 and 3 demonstrated that normal or high levels of serum B12 do not necessarily mean efficient utilisation of B12 at a cellular level. Functional B12 deficiencies can also produce similar pathologies and symptoms. Measurements of MMA and homocysteine levels in all suspected patients is recommended. Levels should generally be measured before B12 replacements as this could potentially produce false negative results. However, once blood tests have been sent there is no need to wait for results before commencing empirical treatments if the clinical suspicion is high.
4. Recreational N_2O use is increasingly recognised as a cause for functional B12 deficiency and SCDC. It is important to remember that patients may not offer the history of N_2O as it is a drug of abuse.
5. Clinicians may forget that N_2O is frequently used in anaesthetic medicine and iatrogenic exposure needs to be investigated carefully where clinical suspicion is high for a functional B12 deficiency.

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Dr Guy Leschziner – The Nocturnal Brain: Nightmares, Neuroscience, and the Secret World of Sleep

I interviewed Dr Leschziner in September 2020, about his new book *The Nocturnal Brain*. It was a virtual interview, Dr Leschziner at work, in scrubs, and myself from home.

I know Dr Leschziner as I have been a Registrar at Guy's and St Thomas' Trust where Guy is a Consultant. I was delighted to read his book, which I found revelatory in terms of my own clinical approach to sleep.

Ann Donnelly, ACNR Co-Editor

AD: Hello, thank you for contributing to ACNR and allowing me the time to interview you. I would like to begin by asking you what it was like to be a full time Neurologist and then also become an author? How did it come about?

GL: A book was never something that I ever had any intention of doing. I had no particular desire to do a book. I ended up doing this radio series for BBC Radio Four on sleep disorders (https://www.bbc.co.uk/programmes/b09jj9t4). After that went out, I got a phone call from a literary agent who asked, "Have you ever thought about writing a book?"

At first I said "No, I don't have the time." He approached me just before the Christmas period, and he said, "You've got some days off. Why don't you just sit down and do a sample chapter and see whether you enjoy doing it."

I sat down for a few days and thought about it. I enjoyed the process and in a strange kind of way, I found it quite mindful. It distracts you from all the stresses and strains of clinical life and you switch off. You focus on something, okay, that's related to your day, but it uses a different part of your brain and makes you think about things in a different way.

I wrote the book in about five or six months at weekends, in the evenings and any sort of spare moments and found it enjoyable. The aftermath of writing it has been enjoyable as well.

AD: What did you do when you encountered your blank page, did you just dive in and get on with it? It sounds like you were sort of cajoled into it and then you got into the flow. You mentioned Oliver Sacks in your introduction. I've always thought in his books, that he doesn't depict a realistic reflection of the life of a typical Neurologist, because he really got to know his patients outside of the hospital setting and formed deeper relationships with them. Was this a unique opportunity for you to do that in a way? Did you get to know them more than you would ever have done otherwise?

GL: Yes. He (Oliver Sacks) managed to spend an inordinate amount of time with patients and that's a sort of luxury that the modern NHS Neurologist doesn't really have. The advantage of writing this book was that these were patients who, for the most part, I'd already had a long diagnostic or therapeutic relationship with, but I got to know them a little bit better because, quite frankly, when we are in a 30 minute appointment, we don't discuss many of the aspects of their life and how their disorder interacts with that life.

We don't discuss many of the family and social issues that we perhaps should do if we have more time. So this was a fantastic opportunity to meet some of them outside the clinic room.

AD: Absolutely. So that must be enriching going forward with your interactions with those patients.

GL: Yes, absolutely. It was a real privilege and I think that, some of the people who I wrote about in the book, some of the patients are the same patients that I interviewed for the BBC series. I will have interactions with some of them outside of the clinic room even now, because you do form strong relationships with people.

AD: That aspect of your book was interesting, and then from another perspective, you went to look at papyrus from the Egyptian times and examined the history of sleep. So you had a chance to get to know patients, but you also immersed yourself in the history of sleep. Was that because of the book or was that something you would have done anyway?

GL: It's a real indulgence to be able to email the British museum and say "I'd like to examine this old papyrus, which I know you've got in storage. Is there any way that I can have a look because I'm writing a book?" It was quite a lovely thing to be able to do.

AD: Going back to interaction with patients, actors have the fourth wall, which they can sometimes break. In a way there's that wall we have between our patients as doctors. For the book, in a way, you're going around that by meeting patients outside of clinic. Was that in any way complicated at any time?

GL: No. One of the biggest issues that I had to address in writing the book, was that I did not want to threaten my therapeutic relationship with my patients by writing about them. So I tried to include them as much as possible in the process of writing the book. That may have been as little as saying to them, look, here is the chapter, if you are uncomfortable with anything that I write about, or if you want to phrase it in a different way, then let me know, and I will do that. I was upfront with them, right from the start.

AD: That's the opposite of what most writers supposedly do because writers in general are famous for plundering their friends and family for copy. So, would you consider that you had a therapeutic approach to the way you were writing as well?

GL: Essentially I was telling their story. It was their story to tell, I was telling it and putting it into context, putting it into a scientific, or as you say that historical context. I wanted to ensure that that was the relationship, that they didn't feel that I was stealing their story, for them to know that they were still the tellers of their story.

AD: I liked the way each chapter structure begins with a person, then it flows into more general discussion about sleep and the neuro biological basis. You always return to the patient and your conclusions about that. Do you think that in writing this book, you came up with new concepts and were you able to synthesise these big ideas by taking all these strands together and having to write it as a book?

GL: I didn't come up with any new ideas, but I think that's certainly formulated more clearly my views on aspects of clinical sleep medicine. I perhaps analysed more carefully what it is that I do within my clinical practice. In that respect,

it was a process that was not only good for me, psychologically, but good for my development as a clinician.

AD: As a Neurologist, especially somebody who works with patients with traumatic brain injury (TBI), I learned so much from this whole book. I wasn't aware that impaired sleep is classed as a possible carcinogen by the World Health Organization (WHO) and I wasn't aware of the REM sleep association with hypothermia. Having read your book it seems like sleep is an under-explored part of neurology.

GL: The way that sleep medicine was presented to Neurologists was as predominantly 'pure' Neurological disorders, like frontal lobe epilepsy, restless leg syndrome, and narcolepsy. That was the breadth of Neurological interest or expertise in sleep.

Within my own clinical work, which is to make sleep part of a big multi-disciplinary centre, rather than within the confines of a silo of Neurology or Psychiatry – the goal is to try to broaden out that interest on that relevance, not just in Neurology, but to every single specialty.

We now understand the relevance of sleep to TBI patients in terms of cognitive abilities, in terms of behavioural issues. It is also relevant to migraineurs, to the epilepsy population - and a whole range of patients with functional neurological disorders.

AD: The book really beautifully illustrates a lot of sleep pathology. There are things that I think in a way, sleep and hunger are things that we are learning a lot about in terms of environmental and genetic influence.

In the book you discuss a young boy with an abnormal sleep wake cycle, and it was fascinating to think that something so integral to our development can be intrinsically abnormal.

We have been talking a lot about sleep pathology, but I'm sure in Los Angeles, there's a whole group of people who were thinking "How can we hack sleep," too? With lucid dreaming, for example, I can imagine there are ways that that could be used to enhance performance and things like that, but how much are we looking at sleeping in the well population?

GL: I think that there is a great deal of attention among certain areas of the scientific community about optimising sleep, particularly when it comes to thinking about ageing. You'll be aware of this growing literature that suggests that slow-wave sleep in particular is involved in metabolic regulation of the brain. It may be that sleep may be an independent risk factor for dementia. We are a long way away from clearly demonstrating a causal relationship, but as a result of that and as a result of our knowledge of sleep and the regulation of, for example, the immune system or metabolic aspects of health like hypertension, people are looking at sleep as part of - for want of a better term - 'wellness.'

I can definitely imagine how people will be thinking, "How can I harness the potential of this in some way?" There are some interesting developments. There are teams looking at potentiating slow wave sleep looking at brainstem evoked potentials and using pink noise. Pink noise is like white noise, but it has a slightly different spectrum of sound. They have timed the frequency of noise to slow wave brain oscillations and they see whether or not there's an improvement, both in the depth of slow wave sleep and whether or not there's an improvement in cognitive tests. Early evidence suggests that there is some improvement in slow wave sleep. There are some so far non-significant improvements in various aspects of cognitive testing.

So that's one example of hacking. I write about how it is possible to stimulate increased lucidity of dreaming by stimulating the parts of the frontal cortex. Could that be a way of first of all, having a more interesting night's sleep, and secondly, could that facilitate learning? Could that facilitate clinical treatments like treatments for nightmare disorder in the context of PTSD, for example? There are a lot of people paying close attention to the technologies that are now available, that may allow us to potentiate certain aspects of sleep.

AD: Having read this book, I feel like I've probably not really touched the surface of most of my patients' sleep difficulties and I'm probably missing a lot and I'm probably not prescribing. How can we improve our clinical approach to sleep?

GL: For a Neurologist essentially if somebody reports poor sleep, then what you need to understand is - is this patient sleep deprived? Is this patient an insomniac, or could there be some biological sleep disorder underlying that? You don't necessarily need to work out what the biological problem is.

If somebody says that they feel sleepy, but when given the opportunity to sleep can't, then that suggests they've got insomnia. If they feel sleepy, but when given the opportunity to sleep, they sleep, and when they increase their duration, they feel better - typically somebody who has a lie in at the weekend - it means that they are behaviourally sleep deprived. That is probably the commonest clinical picture of all. Anybody who is excessively sleepy, despite fully adequate amounts of time in bed, needs investigation for a sleep disorder.

AD: I've been a Junior Doctor and I've been a parent to young children. After years of disrupted sleep, what happens to your intrinsic sleep architecture and can you ever get back to where you were? It's a light-hearted question really.

GL: I think most parents will say that they're never the same again, and we all get a bit older as well, so it changes. We don't have another version of ourselves without children which we can compare to. The genetic contribution to our sleep, both in terms of our sleep duration, our sleep requirement, our resistance to sleep deprivation, our chronotype - pretty much every aspect of sleep has a strong genetic determinant.

Whether our sleep is fundamentally altered by a long period of disruption - I think even that is predetermined because if you have a tendency towards poor quality sleep or a tendency towards insomnia, then having your sleep altered by on-calls and children probably means that your sleep will never be the same again.

AD: How much is technology influencing the quality of our sleep?

GL: Hugely. Work is encroaching on our lives much more than it used to, and that is to a large extent through technology. Both of those things are conducive to worsening sleep.

AD: How big a role does caffeine play or is that partly genetic as well?

GL: I think it's certainly genetic, about 10% of individuals carry a mutation which means that caffeine does not affect their sleep whatsoever. Once again it depends on how good your brain is at initiating and maintaining stable sleep. So if you don't have that particular polymorphism and you are sensitive to the effects of caffeine and depending on what your background sleep is and how much we drink.

AD: We're coming towards the end of the interview, so I think what is really fascinating to me is that you've managed to write while working full time as a Neurologist. It's beautifully written, it flows and the structure of it is really easy to follow. It's just a pleasure. I feel it's also opened the door to learning more. Do you think that we need to be doing a bit more about sleep as Neurologists? What do you think Neurologists will be doing with sleep in 10 years time?

GL: There will be a lot more research into the association between sleep and Neurological disorders. As technology improves and we are better able to study sleep at home, the threshold for investigating people with sleep disorders will be lower. It will become more decentralised. The Neurologist in a standard outpatient clinic will be more easily able to study sleep in a clinical way, but that does need to be accompanied by education in sleep and I guess that's the job of people like me and my colleagues to do that.

Interviewed by:
Ann Donnelly,
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Intracranial tuberculoma and the challenges of global neurosurgery

Abstract
In a world of increasing globalisation, Neurosurgeons need to be able to diagnose and treat neurosurgical conditions which may not be common to the local population. To illustrate this, we describe the case of an intracranial tuberculoma presenting in the post-partum period. Tuberculosis (TB) is a widely recognised mimic of other conditions, including high grade gliomas, which can result in diagnostic delays. We highlight clinical features that should increase the index of suspicion for TB and create a low threshold for trial of empirical treatment. We also discuss educational partnership strategies that may help facilitate global perspectives in neurosurgical training.

Key take home points:
1. Global prevalence of central nervous system tuberculosis is high but is concentrated in certain parts of the world.
2. Rapid diagnosis of central nervous system tuberculosis is essential for optimal management, and requires a high index of suspicion.
3. Risk factors for tuberculosis include being immunocompromised and having been born or having lived in a high TB prevalence country including the Indian subcontinent. This case report highlights pregnancy as a potential time for TB to manifest.
4. Neurosurgical knowledge should be global as well as local, given trends towards international travel and globalisation; collaborative educational initiatives are encouraged to develop this.

Tuberculosis (TB) is a major global health concern. It is one of the top ten causes of death worldwide and the leading worldwide cause of death from infection [1], with approximately 10 million new cases in 2017 alone [2]. Although the majority of TB cases occur in the highest burden countries, it remains a public health issue throughout the world, particularly given the upward trend in worldwide migration rates. Intracranial involvement, either as tuberculous meningitis, tuberculoma or spinal cord tuberculosis, occurs in around 1% of TB cases [3] although the incidence of TBM varies geographically and may not always be reported [4]. Treatment with anti-tuberculosis medications is generally effective for patients with pulmonary TB, and it is estimated that between 2000 and 2017, 54 million lives were saved through correct diagnosis and treatment of TB [2]. However, CNS TB including TB meningitis (TBM), tends to have less favourable outcomes, particularly in cases of multidrug resistant disease or when associated with HIV-1 co-infection [4].

TB is well recognised as a mimic of other conditions, and an atypical presentation in a country such as the UK where TB incidence is relatively low can lead to diagnostic uncertainty. Furthermore, conventional diag-

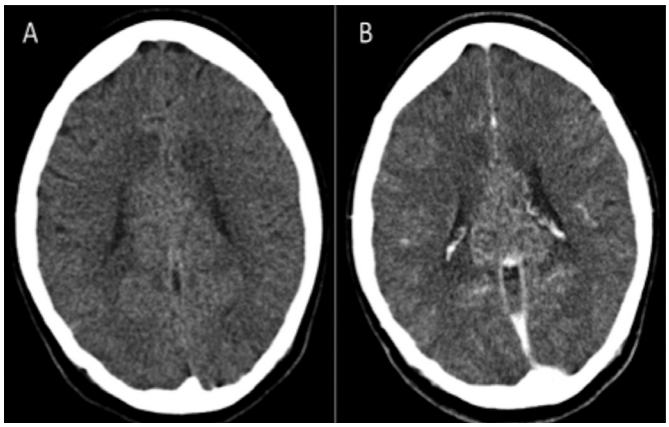

Figure 1. Pre-contrast (A) and post-contrast (B) CT head scans showing an enhancing lesion centred on the corpus callosum.

nostic techniques such as CSF smear tend to have low diagnostic yield, and prolonged waiting for culture results before commencing treatment can have irreversible consequences for the patient. We describe here the post-partum presentation of an intracranial tuberculoma, which closely resembled a high grade glioma on imaging. In the discussion, we highlight risk factors for TB and discuss educational strategies to incorporate the management of TB and other globally relevant conditions into neurosurgical training programmes in regions where trainees are unlikely to gain a rich experience through their own clinical practice but nevertheless may be required to manage critical cases.

Case report

A 30-year-old female, who had emigrated from India six years previously, presented thirteen days post-partum with a two-day history of severe headache, profound short-term memory loss, fever, vomiting and intermittent bilateral limb paraesthesia. Her temperature was 38.8°C at presentation. No cardiovascular, respiratory, abdominal, perineal or neurological abnormalities were detected on examination in the Emergency Department and inflammatory markers were not significantly elevated (white cell count 8.4 x 10^9/L, C-reactive protein 1mg/L). Intravenous fluids and intravenous antibiotics were prescribed to cover possible obstetric-related sepsis, and, following medical review, the patient was discharged home. However, she was readmitted within hours, following a brief unexplained loss of consciousness lasting around two minutes.

Following readmission, a CT brain scan was performed, revealing a lobulated mass arising from the corpus callosum, extending laterally into both cerebral hemispheres and inferiorly as far as the upper midbrain. There was heterogenous enhancement with contrast and extensive vasogenic oedema (Figure 1). An urgent neurosurgical referral was made. The patient was started on dexamethasone. An MRI scan demonstrated appearances strongly suggestive of a primary malignant brain tumour, with peripheral enhancement within the mass and no evidence of restricted diffusion to suggest pyogenic abscess (Figure 2). No hydrocephalus was noted but the third ventricle was deviated to the right of the midline. Plans were made to biopsy the lesion. A CT scan of the thorax, abdomen and pelvis was normal with the exception of asymmetric enlargement of the right breast and small volume lymph nodes in the mediastinum and right hilum.

A biopsy was scheduled the following week. The finalised report described non-specific chronic inflammation and reaction with no evidence of pyogenic infection, TB or neoplasia. CSF was also sent for analysis. The cytology result was negative but the sample was retained for culture.

The patient underwent marked cognitive decline 2 days post-biopsy, with no response to increased dexamethasone. Repeat CT was unremarkable. Over the next few days, she continued to decline, with hydrocephalus (requiring two EVDs), followed by diencephalic/upper brainstem swelling, which ultimately led to her death. Post-mortem identified the cause of death to be raised intracranial pressure secondary to basal tuberculous meningitis and tuberculoma, and the CSF that had been cultured revealed Mycobacterium tuberculosis after 12 days, which was after the patient's death.

Discussion

This case describes an intracranial tuberculoma with imaging features closely resembling a high grade glioma. These imaging features combined with the lower incidence of intracranial TB compared with high grade glioma tumours in the UK led to diagnostic delays. In this case the low diagnostic yield of CSF testing and prolonged culture time meant that the patient had died before a diagnosis was reached. The case highlights the importance of maintaining a high index of suspicion of TB in patients from countries where TB is endemic, and having a low threshold for obtaining an infectious disease consult and starting empiric treatment when there is suspicion of TB or biopsy results are not supportive of neoplasia. The following discussion aims to outline key aspects in the history and examination that could point to a diagnosis of TB, discuss guidance about the management of intracranial TB and consider how to integrate TB and similar conditions into the neurosurgical education of trainees who may not live in endemic areas.

Successful treatment of tuberculoma requires prompt diagnosis, initiation of anti-tubercular therapy and consideration of the need for adjunctive surgical intervention. According to the British Infection Society guidelines, tuberculoma should be suspected in any patient with risk factors for CNS TB presenting with symptoms or signs of CNS tuberculoma (including headache, seizures, focal neurological deficit, fever, vomiting or weight loss). Risk factors for TB include HIV or other form of immunocompromise, having been born or lived in a high TB prevalence country, or recent contact with pulmonary TB [3]. Pregnancy and the post-partum may also represent a vulnerability to CNS tuberculoma, and the post-partum period is a particularly common window in which TB manifests in peri-partum females [5]. Modulation of the host proinflammatory response occurs during pregnancy [6] followed by rapid reversal of these changes after delivery, which can result in accelerated progression of previously latent or quiescent infections, including TB [7]. Presentation of TB at extra-pulmonary sites may be more prom-

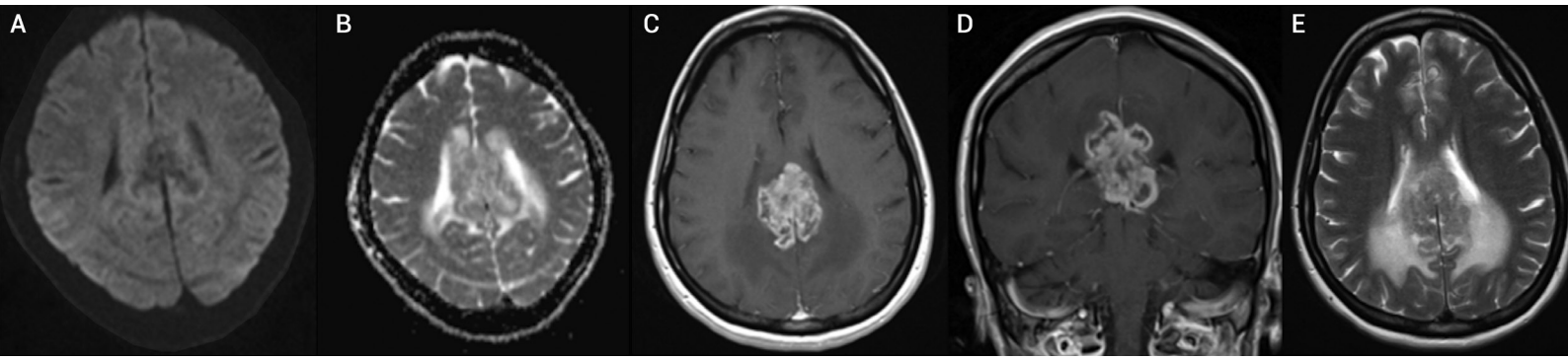

Figure 2. Diffusion-weighted image and ADC map (A, B) with no evidence of restricted diffusion. C: T1 axial post-contrast, D: T1 coronal post-contrast, E: Axial T2 images demonstrating the lesion with peripheral enhancement within the mass.

inent in pregnancy and the post-partum period, including the CNS [8,9].

In 2018, the WHO recorded approximately 10 million new cases of TB. Two thirds of these cases were in six countries (India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa), while only 3% of cases were in the WHO European region and the Americas respectively (https://tbfacts.org/tb-statistics/). *Mycobacterium tuberculosis* infection of the central nervous system (CNS) occurs in around 1% of all cases of TB [3], and tuberculomas (parenchymal granulomas) occur in up to 50% of patients with CNS tuberculosis according to a recent case series [9]. Based on the WHO statistics for 2018, this would equate to about 1500 new cases of CNS tuberculoma annually in each of the WHO European and Americas regions, compared with 135,000 in India alone.

In the UK, between 2000 and 2016 there were on average 236 new cases of CNS TB reported per year, of which approximately 119 per year were classified as having CNS involvement without meningitis (i.e. tuberculoma or other CNS involvement). According to NHS statistics, there are approximately 4500 new cases of primary brain tumours each year in the UK, of which 70-80% are high grade gliomas, thus, statistically, at least 20 high grade gliomas are seen for every case of tuberculoma (far more if it is considered that many tuberculomas will not present to neurosurgery), making glioma the most likely diagnosis given the scan appearances demonstrated in the present case.

Based on this information, CNS tuberculoma is a rare but important diagnosis in the UK, one that neurosurgical trainees in low incidence regions should know how to manage but are unlikely to be able to become competent in managing through experience based learning.

Different approaches could add a global perspective to neurosurgical training programmes in high income countries (HIC) which lack exposure to TB and certain other pathologies. Many neurosurgical departments in the UK have visiting fellows from low- and middle-income countries (LMIC), either employed directly by Trusts, or on specific training fellowships such as through the International Surgical Training Programme (ISTP), part of the wider MTI programme (Medical Training Initiative). Similar schemes are operational in other HIC [10]. One approach would be to encourage visiting international fellows from LMIC to deliver case-based teaching based on neurosurgical practice in their home countries, selecting important pathologies that are rare but nonetheless relevant to HIC, but are that are seen more commonly in the LMIC setting. This would benefit the fellow as it would develop their teaching experience, as well as bringing a global perspective to routine departmental teaching.

Online platforms and social media feeds are increasingly contributing to neurosurgical learning. For example, educational resources such as The Neurosurgical Atlas are available for trainees to access around the world, and many training systems have an online component to supplement face-to-face learning, such as the UK ebrain learning system (http://www.ebrain.net/). Developing the global health components to these learning interfaces to reflect the workload of the global neurosurgical workforce would allow key information and case studies to be accessible to learners around the world, and enable the developers of the learning programmes to gain recognition as leaders in health education and innovation.

Finally, some neurosurgical units have developed twinning ventures or partnerships with a unit in a different part of the world, either holding clinical exchanges or carrying out collaborative research. Traditionally the direction is from an HIC to an LMIC. Building case-based-teaching into twinning ventures, via online platforms such as Skype or Zoom would allow the entire units to benefit from the connection, rather than the smaller number of surgeons directly engaged in the exchange. It would be likely to result in bilateral transfer of knowledge; enhancing training in both participating units, at relatively low cost.

Traditionally the development of these collaborations has been challenging due to various factors including lack of institutional support, lack of funding and lack of recognition for academic aspects of global surgery [10]. However, prioritising mutual development and shared learning across national and international boundaries follows the directive of the UN Sustainable Development Goals (SDGs), and in an increasingly interconnected world we suggest that intentionally developing international and globally focused neurosurgical learning communities will enhance both surgical training and patient care.

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Pourfour Du Petit and the cervical sympathetic nerves

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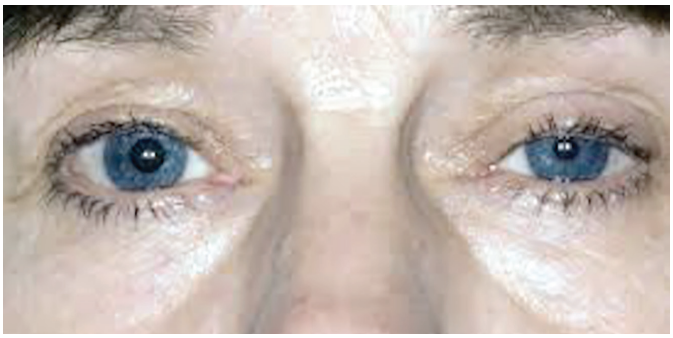
Abstract

François Pourfour du Petit (1664-1741) was a Parisian experimental Neuroanatomist, and Ophthalmologist. Based on his extensive experiences of brain and spinal injuries as a military doctor in the armies of Louis XIV he performed many animal experiments that demonstrated the anatomy and functional significance of the cervical sympathetic nerves, correcting previous errors of Thomas Willis and Raymond Vieussens.

He long predated the descriptions of Horner's syndrome (1869) when he showed that interruption of sympathetic pathways inactivated both the dilator muscle and produces miosis, and the superior tarsal muscle, which produces ptosis and enophthalmos. This was later elaborated by Hare, Weir Mitchell and Claude Bernard.



The tetrad of ptosis, miosis, enophthalmos, and impaired facial sweating (Figure 3) was described in 1869 by Johann Friedrich Horner (1831-1886) (Figure 1), Professor of Ophthalmology in Zurich.

The tetrad of ptosis, miosis, enophthalmos, and impaired facial sweating was described in 1869 by Johann Friedrich Horner (1831-1886) (Figure 1), Professor of Ophthalmology in Zurich:

> *Anna Brändli, aged 40, a healthy looking peasant woman…six weeks after her last confinement noticed a slight drooping of her right upper eyelid, …The pupil of the right eye is considerably more constricted than that of the left, but reacts to light; the globe has sunk inward very slightly…During the clinical discussion…the right side of her face became red and warm; while the left side remained pale and cool. …The patient thereupon told us that the right side had never perspired,… the thermometer on the right recorded 35°C. that on the left, 30°C.…" [1,2]*

Figure 1: Johann Friedrich Horner.

Horner's syndrome (oculosympathetic paresis) had been described several times before his report. Edward Selleck Hare, in 1838, and Silas Weir Mitchell both gave earlier accounts: Hare's in a cervical tumour, Weir Mitchell's in a gunshot neck wound [3].

The sympathetic nerves

Long before these descriptions, the anatomy and function of the sympathetic chain had been studied but mistakenly represented. It is easily forgotten that at this time there was little scientific or rational scientific medicine. The era was of magic, miasma and witchcraft. Insubstantial ideas of the spiritus animalis were rife, and irrational speculation abounded.

The sympathetic chain was known as the *intercostal nerve*, a name introduced by Thomas Willis (1621–1675). He described:

> *The principal trunk of the intercostal nerve as consisting of two or three twigs, which were sent back from the fifth and sixth nerves, and joined together as in one stem [4].*

Thus he believed the sympathetic *descended* from these cranial nerves along the rib cage: hence his term intercostal. Similarly, Raymond Vieussens (c.1641-1715), a distinguished anatomist and pathologist from Montpellier and physician to the Hospital of St. Eloys described the ophthalmic branch of the fifth cranial nerve as:

> *Emitting, sometimes one, sometimes two fibres, which with a fibre emitted from the sixth cranial nerve became attached to the intercostal nerve [5,6].*

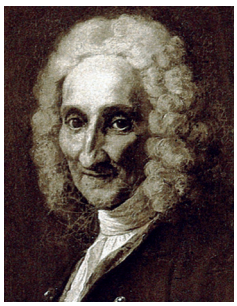


Figure 2: Francois Pourfour du Petit.

François Pourfour du Petit (1664-1741) (Figure 2), a Parisian experimental Neuroanatomist, and Ophthalmologist refuted these accepted ideas. He had scrutinised and investigated his extensive experiences of brain and spinal injuries as military doctor in the armies of Louis XIV between 1693 and 1713. He verified his conclusions by many animal experiments. In this way he demonstrated the anatomy and functional significance of the cervical sympathetic chain.

In 1727 Du Petit described the *intercostal nerve as ascending*, entering the skull along with the carotid artery in the twisted petrous tube [7]. Crucially, he recognised the preganglionic fibres arising from T1 to L3 spinal segments. Thus, he disproved both Willis and Vieussen's identification of the origin of the sympathetic chain in the fifth and sixth cranial nerves. Although du Petit's results were unequivocal, lamentably they remained latent, largely ignored until the nineteenth century.

In 1727, he reported that cutting the superior sympathetic nerves of dogs produced ptosis and miosis [7].

His later dog experiments convinced him that miosis was due to connections between the ciliary nerves with the intercostal nerves. He showed that interruption of sympathetic pathways (oculosympathetic paresis) inactivates both the dilator muscle and produces miosis, and the superior tarsal muscle, which produces ptosis and the appearance of enophthalmos. This contrasted with third nerve palsy where ptosis

and a dilated pupil result from a loss of innervation to the sphincter pupillae.

In a soldier whose neck had been slashed by a sword he described dilatation of the pupil (mydriasis) eyelid retraction, and hemifacial hyperhidrosis – the *syndrome of Pourfour Du Petit* – in effect a reverse Horner's syndrome. He experimentally confirmed this signs in dogs by cutting their cervical sympathetic chain.

He also showed with originality that brain injuries could cause weakness or paralysis of the contralateral limbs, and he established the medullary decussation of the pyramidal tracts.

Pourfour du Petit-Claude Bernard-Horner syndrome

There are few eponyms more clumsy and confusing than the '*Pourfour du Petit-Claude Bernard-Horner syndrome*', each with disputed demands for priority [8]. The history of Petit's clinical observations and experiments, though thoroughly recorded by Best [6], failed to achieve recognition. In 1851 Claude Bernard using rabbits repeated and confirmed his conclusions and gave his own distinctive description [9].

The nomenclature unsurprisingly proved polemical. Paul Bonnet's paper [10] fiercely defended the eponym of Pourfour du Petit instead of Horner:

> *Il est temps que le nom de Horner – tout au moins en ce qui concerne le syndrome paralytique du sympathique – rentre dans l'ombre, d'ou il n'aurait jamais du sortir". [It is time that the name of Horner – at least with respect to the paralytic syndrome of the sympathetic – returns to the shadows, which it should never leave again].*

Of the original run of 200 copies of du Petit's pamphlet – *Lettres d'un medecin des hôpitaux du roy, a un autre medecin de ses amis* – only three copies remain. This may explain why citations to his work are sparse. One copy is in the Bibliotheque Nationale, and there was a "London copy" photographed by William Osler [11].

Sympathetic denervation hypersensitivity in the first, second, or third order (pre-postganglionic) fibres can be shown with the aid of cocaine and adrenaline installations, to localise the lesion. The many causes are disclosed by associated neurological symptoms and neuroradiology.

Whereas du Petit and Claude Bernard experimented mainly in animals, reference to oculosympathetic paralysis in man was recorded but uncommon before Horner. For his detailed clinical account he deserves full credit.

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George Smith: A historical vignette

By Nikhil Agarwal, and Pragnesh Bhatt

Dr George W Smith was an American Neurosurgeon who pioneered the famous Smith-Robinson procedure of anterior cervical discectomy and fusion. Furthermore, he has been credited with developing the vessel encircling aneurysm clip, the automatic drill and a treatment for trigeminal neuralgia with Stilbamidine. This brief article looks back at his great achievements.

Dr Smith was born on December 4th 1916 in Deer Creek, Minnesota. He gained his Bachelor of Science degree from the University of Indiana in 1939, after which he proceeded to gain a Doctor of Medicine from the School of Medicine in Indianapolis in 1942 [1].

Dr Smith completed his internship years at Gorgas Hospital, which was an army installation in Panama. He was a Physician for the United States Army during World War 2 from 1944-1946. During his time in the war, Smith gained significant experience in spinal injuries. He took this knowledge with him and continued his medical training as a resident in the University of Maryland. He later became an instructor at the University of Maryland in 1950, for two years.

Smith was subsequently appointed as an instructor at John Hopkins University. Thereafter he became Assistant Professor in 1953. Later in the same year, he become a Professor and the Chief of Orthopaedic Surgery at John Hopkins University.

During his time at John Hopkins, Dr Smith found that the administration of IV Stilbamidine was an effective treatment for trigeminal neuralgia. This was far safer and cheaper than other potential treatments offered at the time. He noted that the pathology was still unknown and that there were very few successful treatments for trigeminal neuralgia. He conducted a small trial with 14 outpatients, who were given IV Stilbamidine. The patients noticed that the severity of their pain and the number of attacks decreased over time. It was found that complete freedom from pain occurred two to four months after the initiation of treatment. However, during his trial, he discovered that the use of Stilbamidine resulted in a side effect of blunting of corneal reflexes [2]. His treatment, despite its success, was eventually dropped due to the risk of significant toxicity.

While at John Hopkins, Smith met with an Orthopaedic Surgeon, Dr Robert Robinson, and in 1955 Smith and Robinson first described their idea of cervical discectomy and fusion [3]. They continued this work and published their method in 1958 in The Journal of Bone and Joint Surgery. In this paper Smith and Robinson described their experiences with the anterior removal of the intervertebral disc and interbody fusion, with a report of 14 patients [4]. However, in the same year there were two other independent publications of versions of anterior approaches

to the cervical spine. One was proposed by Dereymaeker & Mulier, with the other being proposed by Cloward.

Smith & Robinson's method was an incredible improvement on previous techniques as it did not require any manipulation of the spinal cord. Their method involved removing one or more cervical discs and allowing for the fusion of the intervertebral bodies. However, what made this technique different from the other two which were published in 1958, is that there was no need for direct decompression of the neural elements. In comparison, Cloward visualised and decompressed the spinal cord and removed any osteophytes there. Smith and Robinson assumed that by removing the disc, and fusing the bodies, the osteophytes would be resorbed, and decompression of the skeletal structures was achieved. They then placed iliac bone grafts in the disc spaces and the incision created was then closed [5].

Following their original paper in 1958, a follow-up was conducted and published in 1962. A more comprehensive study and follow-up was conducted which included the results of their first 55 patients [6]. It was found that the fusion rate was around 88%. They concluded that "when other treatment seems impractical, anterior interbody fusion appears to be good surgical treatment for degenerative joint and disc disease of the cervical spine" [6]. This was then followed by another review in February 1969, in which a report on 93 consecutive cases was published in the Journal of Neurosurgery. This included patients who were treated between 1960 and 1964. They found their treatment to be successful, eliminating pain for most patients who were operated on [7].

In June 1956, Dr Smith left John Hopkins to assume his new role at the Medical College of Georgia as Chief of Neurosurgery and Associate Professor. A month later he was promoted to Professor. During his time at the Medical College of Georgia, Dr Smith started working on building a residency programme for the university. Following on from this, he continued his medical research and innovation. In 1960, Dr Smith created the vessel encircling clip for brain aneurysms. This was a very important advancement as it allowed the surgeon to tackle aneurysms on the arterial wall opposite the surgeon, which was previously far more challenging [8].

Dr Smith then moved on to develop the automatic drill. Smith wanted a device which could drill through the skull but stop as soon as it penetrated the last layer of bone. He published his ideas in the Journal of Neurosurgery in 1950 [9]. However, it was much later, on 8th July 1958, that Dr Smith was awarded a patent for his idea of an automatic drill. The simple idea was that once the drill had passed the outer and inner parts of the skull, there is a pressure change. Smith found a way for the drill to detect this change and disengage the drill automatically. He commented that this new drill offered a whole host of advantages to neurosurgery. Smith found that his new drill markedly reduced operating times, with a far more efficient way to open the cranium. The safety of operations was far greater, as there was a much smaller chance of hitting brain matter. Before this invention, surgeons had to take into consideration the thickness of the skull, which differed from patient to patient. However, this became redundant with the automatic drill. It was also found that the drill produced sizeable chips of bone which could be used to fill in the defect created by the drill [10]. These points illustrate how this invention of Smith's may have been his greatest contribution to neurosurgery.

Dr Smith was a man who travelled very frequently and so this led him to obtain his own private flying license, which allowed him to fly his own aircraft. However, unfortunately it was this which led to his untimely demise. In April 1964, on his way to a routine meeting to the Harvey Cushing Society, Dr Smith's plane crashed in North Texas, killing him as well as his wife and mother-in-law [11].

Dr George W Smith has been regarded as one of the key surgeons in the innovation of spinal surgery. His inventions in anterior cervical decompression and fusion, as well as the creation of the automatic drill, are achievements which benefit thousands to this day.

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Migralepsy explained … perhaps?

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What is migralepsy? Etymologically the explanation is simple: a blend or portmanteau word combining "migraine" and "epilepsy". But what about the clinical definition? Does this simply imply an association between the two conditions? Since both are common, some association would be expected by chance concurrence alone. Or does it suggest comorbidity, some shared pathophysiology (both are paroxysmal disorders)? If so, is this to mean a unidirectional link, such that migraine triggers epilepsy? Or could the link be bidirectional, and hence equally reasonably labelled as "epigraine"?

The term migralepsy apparently originates with the American epileptologist William G Lennox (1884-1960) who, in his 1960 textbook of epilepsy, used it to describe the condition in which "ophthalmic migraine with perhaps nausea and vomiting was followed by symptoms characteristic of epilepsy [1]". Examining other authoritative sources, I find no entry in the online Oxford English Dictionary, and the term does not appear in either the ICD10 classification or in the 2017 International League Against Epilepsy (ILAE) classification of seizure types.

The International Classification of Headache Disorders 3rd edition (ICHD3; https://ichd-3.org/) is more helpful, including a category (1.4.4) of "migraine aura-triggered seizure", which, it is acknowledged, is "sometimes referred to as migralepsy". This is defined as a "seizure triggered by an attack of migraine with aura" and has the following diagnostic criteria:

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below
B. Occurring in a patient with 1.2 *Migraine with aura*, and during or within 1 hour after an attack of *migraine with aura*
C. Not better accounted for by another ICHD-3 diagnosis.

The implication here is clearly of a unidirectional process (i.e. epilepsy does not trigger migraine).

The condition is acknowledged to be rare (I cannot recall seeing a case in 20+ years as a Consultant Neurologist). Indeed, fewer than 30 references are recovered on Pubmed when using "migralepsy" as a title word. Diagnostic issues include the risk of misinterpreting occipital lobe seizures as migraine visual auras.

Accordingly, some have argued strongly for the deletion of the term, favouring ictal epileptic headache [2]. But this judgement may possibly be premature. Migraine stroke is rare, but nonetheless not discounted as a plausible diagnostic category. As noted by Miller Fisher in this context:

> Unusual cases [of migraine], while disconcerting to the clinician, have a special importance, for any theory of the mechanism of migraine must explain not only the commonplace but also these aberrant forms; indeed in our current state of knowledge they provide special information and may suggest additional avenues for speculation [3].

In 1991, the philosopher Daniel Dennett published a book entitled "Consciousness explained", but not all readers entirely concurred that this was, as the title might imply, the last word on the subject. In the same provisional, rather than definitive, spirit, I tentatively suggest the following explanation for migralepsy.

When considering the possible pathogenesis of migralepsy, it is of note that, according to ICHD3, "Evidence of an association [of seizure triggered by an attack of migraine] with 1.1 *Migraine without aura* is lacking". Hence, aura would seem to be a sine qua non for migralepsy by this definition, suggesting the possibility of a neurophysiological continuum between migrainous aura and epileptic seizure.

The possibility that migraine aura may be a consequence of the phenomenon of Leão's spreading depression [4] was first suggested by Milner (1958) and then by Lauritzen (1985) and Pearce (1985) [5-7]. It is now widely assumed that this is indeed the mechanism, albeit "cortical spreading depression" is now often characterised as part of a continuum with spreading depolarisation (SD), a wave of electrophysiological hyperactivity followed by a wave of inhibition which propagates across the cerebral cortex at between 1-10mm/min. The changes in neuronal electrical activity are mediated by changes in extracellular ion concentrations, particularly increased K^+, toxic release of glutamate, dispersion of electrochemical gradients from failure of Na^+/K^+-ATPase pumps, mitochondrial dysfunction, and cytotoxic oedema, leading to prolonged neuronal membrane depolarisation and refractoriness to neuronal impulse and synaptic transmission. SD has also been implicated in the neurological sequela of other disease processes, including ischaemia, hypoxia, hypoglycaemia, and epilepsy [8].

The relationship between SD and epileptic activity is complex and poorly understood [8], but certainly in some circumstances SD may facilitate the onset of seizure activity, for example by lowering seizure threshold and/or enhancing spontaneous epileptiform activity [9], or accelerating interictal to ictal transitions [10]. SD might therefore account at a mechanistic level for the neurophysiological continuum between migrainous aura and epileptic seizure, triggering two clinically distinct events sequentially as the wave progresses across the cerebral cortex. This possibility has previously been suggested, the rarity of "migraleptic event" being accounted for by the higher threshold for seizure onset and propagation than for migraine aura-associated SD [11]. The differential thresholds would also explain the much higher frequency of ictal and peri-ictal headaches.

Another example of such a sequential process, with shared pathophysiology but distinct clinical manifestations, may be pertinent to this argument. Episodes of transient global amnesia (TGA) are reported on occasion immediately to precede a typical migraine headache, prompting the suggestion that TGA may sometimes be a form of migraine aura. Because of its relationship to migraine, both clinical and epidemiological, TGA has also been suggested to be a consequence of spreading depression [12,13] or, more recently, SD [14]. The rarity of this occurrence may reflect the lower susceptibility of the hippocampus to develop SD compared to other brain regions, the occipital cortex being the most vulnerable area [15].

Shared mechanisms might also contribute a possible explanation for the rare occurrence of migraine stroke or, as per ICHD3 terminology, migrainous infarction (category 1.4.3. One or more migraine aura symptoms occurring in association with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging, with onset during the course of a typical migraine with aura attack). Again, as for migralepsy, this definition indicates that aura is a sine qua non, suggesting the possibility of a neurophysiological continuum between

migrainous aura and infarction. The haemodynamic response to SD is variable, including both monophasic hypo- or hyperperfusion and biphasic vasoconstriction and vasodilation [8]. A profound SD-related hypoperfusion in the appropriate vascular territory might therefore account for ischaemic infarction associated with migraine aura. This possibility has also been previously suggested [16]. Migraine aura has on occasion been reported as the only symptom of neuroradiologically-confirmed ischaemic stroke [17].

These considerations, even if wrong, highlight the importance of looking at mechanisms, and the possibility that "aberrant forms" of migraine may shed light on theories of mechanism, as Miller Fisher presciently suggested [3]. In this context, it has been suggested that SD may be a "universal principle" of lesion development [18]. If so, this mechanism might underpin different paroxysmal clinical phenotypes (aura, seizure, amnesia, stroke). An argument for such a biology-first approach, agnosic to phenotype, with secondary definition of patient subgroups according to biomarkers, has previously been advocated for neurodegenerative diseases such as Parkinson's and Alzheimer's, even though this segregation may not result in homogeneous clinical clusters [19]. Maybe this will be the way Neurology is pursued in the future.

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The Last Act of Love

I recently joined a virtual meeting hosted by Cardiff Neurology Book Club. The book discussed was *The Last Act of Love*, a memoir written by Cathy Rentzenbrink [1]. It tells the story of her younger brother Matty, who sustained a traumatic brain injury following a road traffic collision and was left in a persistent vegetative state.

In the book, she describes her experience of Matty's journey and the difficult decisions faced, how the injury changed her relationship with him, and how it changed relationships with their parents. Rentzenbrink intimately explores the consequences of Matty's brain injury, the impact it has had on her life, and how she came to terms with what happened. As such, the book provides a privileged insight into the effects of an individual's brain injury on their family.

A key point conveyed was of the effect bereavement has on siblings. Commonly, grief support and counselling is focused on parents (or spouses) of the deceased, which risks overlooking the siblings. The author recalls family and friends asking her for updates on Matty's condition, so as not to upset their parents. Her grief was made to feel somehow less valid; she was forced to put on a brave face and stay positive. As a result she avoided her own struggle to cope with what might have become overwhelming feelings of guilt and grief. She also felt she should not complain about the situation, for fear of adding to the burden on her parents. It is perhaps Rentzenbrink's ability to explore her feelings, both of guilt and grief, that gives the story as a whole its power, and its distinctive value.

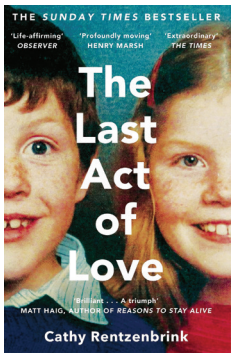
Our group discussed the idea that siblings often only know their life together, and that this made adjusting to the 'new Matty' a challenge for his sister. By contrast, their parents will have known a life before Matty's birth. This discrepancy is something that might increase the difficulties for siblings after catastrophic loss.

The family's initial relief when Matty survived gradually turned to sorrow, as they saw his condition deteriorate after the initial stabilisation. Cathy felt her brother would not want to exist in a vegetative state, leading slowly to a realisation that it might have been better if he had died. She goes on to suggest that if you were to plot grief on a graph, it would look like an undulating wave rather than a straight line; grief is not linear. This analogy resonated strongly with us as a group and allowed us to gain an insight into the long-term effects of sibling loss.

The author also highlights the general lack of awareness and understanding surrounding the effects of significant traumatic brain injury. Persistent vegetative state is poorly understood by the public, and patients with this diagnosis rarely progress to a significant recovery. However, friends and family had expectations that Matty must be better and back to normal because he was at home. Their expectation of him suddenly waking up, had perhaps been fed by stories from fiction, or from the media.

The Royal College of Physicians' guidance on prolonged disorders of consciousness (2013; 2020 update) supports healthcare professionals and families in making difficult decisions regarding ongoing treatment early on in such patients' journeys [2]. This document provided reassurance for Rentzenbrink as she realised other families had experienced similar situations, and she felt that not prolonging Matty's suffering was their 'last act of love'.

This book has certainly had an impact on my thinking and, I believe, will impact my future practice. As a medical student, I am now more aware of the vital importance of offering support to all family members and the importance of addressing their expectations at an early stage. As a group, we would recommend the book to all healthcare professionals likely to encounter severe brain injury and its debilitating effects both on patients, and families (consisting as they do of many members). We also felt that Rentzenbrink's uplifting spirit, despite such a devastating and catastrophic events, provides hope for families experiencing such loss or trauma; this book could be a comfort to those in grief.



Author: Cathy Rentzenbrink
Publisher: Picador
Price: £8.99
Pages: 256
ISBN: 978-1447286394
Reviewed by: Anna Capey, Medical Student, Cardiff University, UK; Harsh Bhatt, Neurosurgical Registrar; Rhian Capey, Traumatic Brain Injury Clinical Nurse Specialist.

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PODCAST REVIEWS

ACNR's 20th Anniversary Podcast

It is a great pleasure to mark ACNR's 20th anniversary with a new departure for the reviews section. This is our first podcast review. And what better inaugural podcast to review than ACNR's very own, in the form of an interview by Sri Kodali.

Sri questions no less a pair than Rachael Hansford, ACNR publisher for the entirety of its first 20 years, and ACNR's founding editor, Professor Roger Barker.

I hope I may be forgiven for throwing all objectivity and caution to the wind, and saying that I thought it was absolutely great. Seriously though, it really was.

This was a delightful half-hour of two friends enjoying a bright and breezy yet erudite conversation, with a few judicious prompts from Sri, and an occasional 'mensh' for such luminaries as Alasdair Coles and Mike Zandi.

Regaining my composure, I can say objectively that it's all very well produced and well presented.

And what a great story! These are people who have found a way of working on stuff they enjoy. Better still, it's a story of being proactive with pragmatism to create something worthwhile...ACNR. I thought it was a mini masterclass in managing, and avoiding, both undue hesitancy and excess risk.

This podcast encompasses life, brain, anxiety, motivation, and joy, and of course it's all Neuroscience.

https://open.spotify.com/show/2LMihQIX9bvMI7wnsdC5id

Reviewed by: Rhys Davies, Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Yssbyty Gwynedd in Bangor, North Wales, UK.

Disease modifying treatments for Parkinson's disease – an update

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Abstract
An improved understanding of the pathological processes leading to neurodegeneration in Parkinson's disease (PD) is leading to the development of a number of disease modifying agents. These include both novel and repurposed drugs. Some of these disease modifying therapies act on cellular targets that have been identified by genetic mutations, while others act on other cellular process which we know are affected in PD. This review provides an update on the progress in the field, and highlights some areas of special interest.

Introduction

Current treatments for Parkinson's disease (PD) are primarily symptomatic and consist mainly of dopamine replacement therapy, and deep brain stimulation. These treatment strategies have gradually improved over the last few decades, and further advances are underway [1], but they do not address the fundamental problem of progressive neuronal loss in the nigro-striatal pathway and other brain regions. New disease modifying treatment approaches are in development that target the cellular events leading to neuronal loss, in order to slow or reverse this process. While this would be transformative, the optimal approach to achieve this is clouded by several unanswered questions. We do not fully understand the function of normal, soluble alpha-synuclein. Furthermore, the exact role played by pathological aggregates of alpha synuclein in pathogenesis is debatable. We do not know whether treatments targeted against genetic subtypes of PD will be effective in sporadic PD [2]. Overall, the research field is very active, studying targeted therapies related to genes, and treatments related to metabolism/mitochondrial function, inflammation, oxidative damage, and neurotrophins [3]. In this review, we summarise the current developments in this field, with a focus on treatments that are in clinical trials. We have selected highlights from a comprehensive list of ongoing studies [3].

Alpha Synuclein

Treatments designed to modulate the aggregation and deposition of alpha synuclein are clearly promising, given the almost universal detection of this pathological process in PD. This approach builds on extensive knowledge obtained since the identification of alpha synuclein gene mutations as the first genetic form of PD, and the detection of dense alpha synuclein deposits within Lewy bodies. Treatments in development aim to prevent or remove excessive alpha synuclein that exists in pathological 'clumped' form of oligomers and fibrils, in distinction from the normal unfolded form of monomers and tetramers. These toxic forms of alpha synuclein impair degradation pathways and cause dysfunction of mitochondria and endoplasmic reticulum [1]. Clinical trials involving antibodies against pathological alpha synuclein are currently in Phase 2. This involves either passive immunisation e.g. infusion of a monoclonal antibody (mAb), or active immunisation such as with PD01A, where the patient's immune system generates antibodies against abnormal alpha synuclein. Prasinezumab (PRX002) is still in development, despite a negative primary outcome in a phase 2a study, on account of a positive secondary outcome of reduction in motor function decline. Cinpanemab (BIIB054) failed to meet its primary and secondary outcomes and has been discontinued at present. Another approach is the reduction of alpha synuclein synthesis using anti-sense oligonucleotides, but this may disrupt its normal physiological role in synaptic transmission and intracellular trafficking [1]. Enhancing the clearance of alpha synuclein, which occurs via the ubiquitin proteasome and autophagy-lysosomal pathways, is also a potential treatment approach, with an aim to restore the balance between benign and toxic forms of alpha synuclein [1]. One strategy is the therapeutic inhibition of the tyrosine kinase ABL, an enzyme that is pathologically activated in patients with PD. Such inhibition would prevent the phosphorylation (and thereby inactivation) of parkin, which normally contributes to cell clearance processes. Nilotinib – an ABL inhibitor used in haematological cancer – has shown some promise in animal models and a pilot study of PD. However, it was ineffective in later stages of PD in one recent study [4]. Radotinib, a molecule from the same class and with higher brain penetration, is also under study [3]. Small molecule inhibitors of alpha synuclein aggregation have the advantage of good brain penetration, and include UCB0599 and anle138b [3,5]. Memantine, a

Table 1. Drugs in advanced stages of development that target molecular pathways not identified through genetic mutation

Drug name/class	Postulated mechanism of action	Stage of development
Glucagon like peptide 1 receptor agonist, eg. exenatide [17,18]	Neurotrophic	Phase 3
Urso-deoxycholic acid [19]	Increased signalling in the Akt pathway	Phase 2
Deferiprone [20,21]	Iron chelation to reduce iron deposition in substantia nigra	Phase 2

NMDA receptor antagonist, reduces intercellular propagation of alpha synuclein [6], and is in a phase 3 study as a potential disease modifying agent using advanced imaging [3].

Glucocerebrosidase

Several new treatments are in clinical development that target mechanisms related to lysosome function, including the enzyme glucocerebrosidase (GCase) that resides largely within the lysosome. Pathological variants in the GBA gene which encode this enzyme are the most common genetic risk factor for PD, being present in around 10% of cases [7]. GCase deficiency has also been observed in patients with sporadic PD [8], so such treatments may be effective regardless of genetic status. The aim is to restore normal lysosome function which is expected to have positive impact on cellular processes, including pathways that assist the recycling or safe disposal of alpha-synuclein [7].

Imiglucerase, a recombinant DNA enzyme used successfully in Gaucher's disease (resulting from different forms of GBA gene mutation) reverses the abnormality in lysosomes in a genetic model of PD [9]. However, treatments for Gaucher's do not cross the blood brain barrier (BBB) and therefore alternative approaches are being developed for PD [10,11]. These include enzyme replacement therapy, enhancement of the activity of available enzyme, and substrate reduction therapy. Gene replacement therapy using vectors such as adeno-associated virus (AAV) has shown success in reducing alpha-synuclein accumulation and neurodegeneration in animal models [11]. The PROPEL trial is a phase 1/2 study exploring AAV treatment using imiglucerase in GBA-positive PD. This viral vector is delivered to the brain using magnetic resonance guided focused ultrasound to open the BBB and permit CNS penetration. Another approach is the use of pharmacological chaperones, whose molecular size is small enough to cross the BBB [11]. These improve cell function by assisting substrate proteins to fold correctly, aiding in intra-cellular transport and improving protein degradation. Chaperones can be administered orally, and are generally not expensive [11]. Ambroxol is an expectorant with promising initial results as a PD therapy, and among the pharmacological chaperones is the farthest down the drug development pipeline. In phase 2 clinical studies Ambroxol had a good safety and tolerability profile, and also had good CSF penetration and target engagement [12]. Substrate reduction therapy is another potential approach, wherein reduced glycolipid production results in a rebalancing of the ratio between enzyme activity and substrate. Glucosylceramide synthase inhibitors with good brain penetration are under investigation, following encouraging results in animal models. Venglustat is one such inhibitor that unfortunately failed to show efficacy in a recent trial in GBA-positive PD cases [13].

Leucine Rich Repeat Kinase (LRRK)

Kinase inhibitors which act on LRRK are in development as potential disease modifiers in PD. Mutations in the LRRK2 gene are the most common cause of dominantly inherited PD (10-15%), and are present in some patients with sporadic PD (1-3%, though higher in some populations). LRRK2 mutations in contrast to GBA mutations can be both causative i.e. a single mutation with a large effect, and a risk factor i.e. a single mutation with small effect size and therefore by itself not sufficient to cause disease. Kinase inhibitors are designed to block abnormally increased LRRK2 activity, due to toxic gain of function mutations, rather than loss of gene product [14]. Increased LRRK2 activity is seen, both in cases with LRRK2 mutations, and cases with sporadic PD [15], so treatments could have widespread benefit. LRRK2 plays a role in striatal synaptic transmission, mitochondrial function, microtubule dynamics and ubiquitin proteasome function [14]. Therefore treatments targeting LRRK2 could have an impact on multiple cellular processes; one proposed mechanism is to prevent the LRRK2-mediated phosphorylation of alpha synuclein, which increases its aggregation, and contributes to its propagation along neurons [14]. However, the LRRK2 gene is also expressed in immune cells, kidney, and lung, so monitoring of the effects of kinase inhibition is required to check for adverse effects on other organ systems [15]. Results from a phase 1 study in healthy controls and patients with PD have found no safety concerns with DNL151, a LRRK2 inhibitor, when administered for a 28 day period [16]. Phase 2 and 3 studies are in the pipeline.

Additional treatments

In addition to the treatments outlined above, there are other promising drugs which are in advanced stages of development, and summarised in Table 1.

Conclusion

Current approaches for disease modification are multi-faceted and include both novel and repurposed drugs. While it is impossible to predict which of these approaches will be the most successful, we can surely be optimistic, based on the scale of work that is underway.

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These dates are correct as we go to press. Please see www.acnr.com/event, or check with the organisers for any changes due to the COVID-19 pandemic. Please send diary listings for our website and next issue to Rachael@acnr.co.uk

2021

NOVEMBER

European Charcot Foundation 29th Annual Meeting
14-18 November, 2021; Italy and online
https://www.charcot-ms.org/29th-annual-meeting/

MS Academy Basecamp 2
17-18 November 2021 ; Sheffield, UK
https://neurologyacademy.org/ms-academy

Dravet Syndrome UK (DSUK) 2021 Conference – Professional Day
19 November, 2021; Virtual conference
https://www.dravet.org.uk/events/dsuk-2021-conference-professional-day/

BSCAH Medical Hypnosis for Healthcare Professionals
20 November, 2021; Online – 2 days.
www.bscah.com/book-event/medical-hypnosis-for-healthcare-professionals-weekend-november
E. natoffice@bscah.co.uk

Epilepsy Climate Change
25 November, 2021; Online
https://www.eventbrite.co.uk/e/epicc-epilepsyclimatechange-epilepsy-in-change-tickets-178064364307

West of England Seminars in Advanced Neurology (WESAN) 2021
25-26 November 2021, Exeter, UK
https://wesanmeeting.org.uk/

***NEW DATE* 2021 Spine Society of Australia 32nd Annual Scientific Meeting**
International Convention Centre, Sydney, Australia
26-28 November 2021
www.dcconferences.com.au/ssa2021

DECEMBER

Decisions, decisions – the way forward: supporting capacitous choices in litigation and beyond
1 December, 2021; York, UK
E. janette@babicm.org.uk

Encephalitis 2021
7 December 2021
Royal College of Physicians, London (and virtual)
www.encephalitis.info/conference

Parkinson's Advanced MasterClass 40.2A
7-8 December, 2021; Sheffield, UK
https://parkinsonsacademy.co/events/

The Dizziness and Balance Workshop
8 December, 2021; London, UK
http://dizzinessandbalanceworkshop.co.uk/

MS Foundation MasterClass
Module 2: December 2021,
Sheffield University Campus, UK
https://multiplesclerosisacademy.org/courses/foundation-masterclass/

2022

JANUARY

Advanced Professional Diploma / BSc / Graduate Certificate / PGCert Course in Clinical Hypnosis & Related Techniques
Starting 15 January, 2022
www.bscah.com/book-event/diploma-bsc-conversion-course-clinical-hypnosis-related-techniques
E. hilary.walker@bcu.ac.uk

3 Module Foundation training in Clinical Hypnosis
From 15 January, 2022; London, UK
www.bscah.com/book-event/3modulefoundationtraininglondon2022
E. natoffice@bscah.co.uk

20th Annual King's Neuromuscular Disease Symposium
28 January, 2022; 0900-1300 Online
Register at tinyurl.com/KNMS2022
Administrator: kch-tr.KNMS@nhs.net

MARCH

3 Module Foundation training in Clinical Hypnosis
From 2 March, 2022; Hybrid (Virtual & Edinburgh)
www.bscah.com/book-event/3modulefoundationtrainingnortherncounties2022
Contact: natoffice@bscah.co.uk

2022 Sheffield Fundamentals of Neuroradiology Course
March 2022, Sheffield, UK
https://fundamentalsofneuroradiology.com/

The UK Neuro-ophthalmology Society (UKNOS) Annual Meeting
17 March 2022; Sheffield, UK.
For details see https://uknos.com

CONy 2022
24-27 March, 2022; London, UK
https://cony2022.comtecmed.com/

Neurology 2022: leading edge neurology for the practising clinician
24-25 March, 2022: Online
23 March, 2021: Pre course symposium: Preparing for the Speciality Certificate Exam; Online
www.ucl.ac.uk/ion/neurology-2022-leading-edge-neurology-practising-clinician
E. d.blundred@ucl.ac.uk

APRIL

EAN Regional Teaching Course
24-26 April 2022, Liverpool
https://www.ean.org/RTC-in-Liverpool-UK.4286.0.html

MAY

8th European Stroke Organisation Conference (ESOC)
4-6 May, 2022; Lyon, France
https://2022.eso-conference.org/

ILAE British Branch 18th Specialist Registrar Epilepsy Teaching Weekend
14-15 May, 2022; Birmingham, UK
https://www.epilepsyteachingweekend.com/

The ABN Annual Meeting 2022
17-20 May, 2022; Harrogate, UK
https://www.theabn.org/page/annualmeeting2022

JUNE

6th World Parkinson Congress
7-10 June, 2022; Barcelona, Spain
E. info@worldpdcongress.org
www.worldpdcongress.org

JULY

15th International Neurotrauma Symposium
17–20 July 2022 • Berlin, Germany
https://www.neurotrauma2022.com/

RehabWeek 2022
25-29 July, 2022; Rotterdam, The Netherlands
https://2022.rehabweek.org/

September

Posterior Fossa Society – First Global Meeting
9-11 September 2022; Liverpool, UK
https://www.delegate-reg.co.uk/pfs2021/

Liverpool Neurological Infectious Diseases Course 2021

Conference details: Tuesday 13 and Wednesday 14 July, 2021 – Liverpool Medical Institution (LMI) – Hosted by Professor Tom Solomon, Professor Nick Beeching, Professor Enitan Carrol, Dr Rachel Kneen and Dr Benedict Michael. ***Report by:*** Brendan Sargent, FY1 at Liverpool University Hospitals Trust.
Conflict of interest: None declared.

In a year during which infectious diseases have enjoyed more than their fair share of time in the spotlight, redoubling of public interest and focus on the efficacy of treatments and public interventions have served as a reminder of how important research in this area is.

Throughout this time exceptional and elucidating work on the neurological impact of COVID has been undertaken, alongside the ongoing tireless work to further our understanding of other neurological infections. This crossroads of two notoriously puzzling specialties promises fascinating and frustrating challenges in equal measure. 'Neurophobia' famously afflicts medical students and Doctors-in-training alike, and this is surely no less the case when the central nervous system is afflicted by infection. Complex interpretation of physical examination, risk-factors, history, and clinical investigations are not made simpler by the infection's impact on consciousness, the central nervous system's inaccessibility, and the bluntness of available imaging techniques.

It has never been more important to develop knowledge, techniques and interest in this area.

The Liverpool Neurological Infectious Diseases Course (NeuroID) has offered a platform for discussion and learning for those interested in this crossroads, since 2007. With an extremely successful history of events, NeuroID has trained over 1000 delegates from over 40 countries, featuring key-note talks and case presentations from clinicians and scientists from many backgrounds, including infectious diseases, neurology, paediatrics, radiology, microbiology and more. It has brought in a huge spectrum of those interested in neurological infectious diseases, from world-renowned experts to the most junior of Doctors at the very start of their careers. By covering common and important presentations as well as rarer cases, the course can interest both ends of this spectrum, offering an update to knowledge, addition to skills and a chance to explore the cutting edge of the field.

In 2021, the pandemic has presented not only a reminder as to why this field is important, but also a clear challenge to the status quo of meetings and conferences. Not to be dissuaded, on the 13th and 14th of July, at the Liverpool Medical Institution, the NeuroID course welcomed 50 delegates from across the UK (the venue was allowed only 50% capacity because of the pandemic), offering teaching on common neurological infections and fascinating discussion on current research as well as more complex and rarer cases.

The first day included a skills update from Dr Maneesh Bhojak from the Walton Centre on radiology in neurological infections, covering reminders for neuroimaging basics to approaches to specific conditions such as

Prof Tom Solomon presenting Prof Nick Beeching with the Richard T Johnson State of the Art Prize.

cerebral toxoplasmosis. We had microbiology teaching from Dr Chris Parry from Oxford, providing excellent tips regarding pathogen identification, and exciting insights into Next Generation sequencing and metagenomics as means to improve diagnostics. Dr Sylviane Defres delivered a talk on meningitis, elucidating some of the more complex sequelae, as well as the rarer causative organisms. The yearly Richard T Johnson keynote lecture was delivered by Prof Nick Beeching of the Liverpool Tropical School of Medicine. His talk, titled 'An Account of the Occasional Neurological Forays of a Peripatetic Infectious Disease Physician, Illustrated with Copious Anecdotes and Reflections' was a wonderful journey through Liverpool's history as an important infectious diseases centre and the broader history of Infectious Diseases as a medical specialty, with leprosy as a case-example, all the while amusing and stimulating discussion with stories and anecdotes. It was a fantastic overarching view of a field's beginnings all the way to where we are now, and a look at what it can mean to be a neurological infectious diseases physician. We also had a selection of cases presented by Dr Benedict Michael, Prof Nick Beeching and Prof Enitan Carol, all of which allowed for some excellent discussion regarding guidance updates to ethical questions. Finally, trainees from across the UK took part in the case-presentation competition. The standard was extremely high by all accounts; Nisha George won the long-case presentation prize and Thomas Locke won the flash-presentation prize with an impressive show of compressing extremely complex cases into very short spaces of time.

As well as high-quality talks and discussion, the NeuroID course offered a fantastic opportunity for networking, with coffee/tea and lunches provided by the very welcoming Liverpool Medical Institute team, and then dinner at Papillon, a local restaurant on the evening of the 13th. For the early-bird and physically active of the attendees, the next morning Prof Tom Solomon (@runningmadprof on Twitter!) hosted a 5km 'sightseeing fun jog'!

Following this, on the second day, we had a fantastic overview of the current state of research into neurological sequalae of COVID from Dr Benedict Michael, including much of the work that has occurred across Liverpool. This prompted lots of discussion, and a look to future collaborative research, highlighted by the individual patient data study, bringing patient data from around the world to inform best practice. Dr Mike Griffiths of Liverpool University then covered meningitis and Dr Nick Davies of Chelsea and Westminster Hospital covered encephalitis. These talks were extremely clinically useful, and provided great hints and tips for clinicians developing their diagnostic acumen in this area. We had a number of cryptic case presentations throughout the day, from Dr Laura Benjamin, Dr Rachel Kneen, Prof Tom Solomon and Dr Mike Griffiths. These covered a range of topics, including the topical PANDAS/PANS which stimulated a lot of discussion regarding the controversy surrounding this diagnosis. Paediatric and adult cases were covered, ensuring a wide range of trainees with varying interests had plenty to gain from the presentations.

Finally, the second day ended with a superb NeuroID quiz, hosted by Dr Nick Davies. The quiz was fiendishly difficult, but extremely enjoyable, with questions pertaining to diagnosing infections on brain MRI (testing how well we had been concentrating!) and questions about Edward Jenner's cow (surely testing obscure infectious diseases knowledge!). It was the perfect way to finish an excellent two days, before delegates and speakers said their farewells. The NeuroID 2021 course was most striking for its ability to both cover basic knowledge as a refresher and context-builder, and covering complex topics and cutting-edge research. From the most junior of Doctors all the way to renowned specialists, we all had plenty to gain from the course, and were also encouraged to give back to the course through discussion and networking. It was an exemplary training course, especially in the manner that it was delivered in spite of restrictions. Speakers were engaging and enthusiastic, but simultaneously all measures to ensure safety of attendees were prioritised. The conveners and organisers did a fantastic job of making everyone feel welcome, and enabled stimulating and exciting discussion at every stage. The course is an absolute must for anyone at any stage in their career, who is interested in the fascinating subjects of neurology or infectious diseases, or their intersection. It is also worth noting that the course offers 10 CPD points for delegate's portfolios.

To find out more about the course, its previous iterations, and to get updates on next year's course, please visit www.liverpool.ac.uk/neuroidcourse and follow @runningmadprof on Twitter!

References: 1. Novartis Pharmaceuticals UK Ltd. Kesimpta® (ofatumumab): Summary of Product Characteristics, Great Britain; April 2021; **2.** Hauser SL, et al. *New Engl J Med*. 2020;383(6):546–557; **3.** Data on file. OMB157 (ofatumumab). Novartis Pharmaceuticals Corp; East Hanover, NJ. December 2019; **4.** Hauser SL, et al. Ofatumumab vs Teriflunomide in Relapsing Multiple Sclerosis: Analysis of No Evidence of Disease Activity (NEDA-3) from ASCLEPIOS I and II Trials. Presented at the 6th European Association of Neurology Congress as Virtual Congress; 23–26 May 2020. Poster LB62; **5.** Migotto M-A, et al. *Neurology*. 2018;90(15 Supplement):P3.406; **6.** Smith P, et al. *Neurology*. 2017;88(16 Supplement):P2.359; **7.** Perrin Ross A, et al. Patient and Nurse Preferences for the Sensoready® Autoinjector Pen Versus Other Autoinjectors in Multiple Sclerosis: Results From a Multicenter Survey. Poster presented at the Americas Committee for Treatment and Research in Multiple Sclerosis Forum 2021; 25–27 February 2021. Poster P210; **8.** Data on file. OMB157 (ofatumumab). OMB 157G 5.3.5.3. Statistical overview. Novartis Pharmaceuticals Corp; East Hanover, NJ. December 2019.

Great Britain Prescribing Information:

Kesimpta®▼ (ofatumumab)

Important note: Before prescribing Kesimpta 20 mg solution for injection in pre-filled pen consult Summary of Product Characteristics (SmPC).

Presentation: Solution for injection in pre-filled pen. Each pre-filled pen contains 20 mg ofatumumab in 0.4 ml solution (50 mg/ml). Ofatumumab is a fully human monoclonal antibody produced in a murine cell line (NS0) by recombinant DNA technology.
Indication(s): Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.
Dosage and administration: Treatment should be initiated by a physician experienced in the management of neurological conditions and the first injection should be performed under the guidance of an appropriately trained healthcare professional. The product is intended for patient self-administration by subcutaneous injection. The recommended dose is 20 mg ofatumumab with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4. *Paediatric population:* The safety and efficacy of ofatumumab in children aged 0 to 18 years have not yet been established.
Contraindications: Hypersensitivity to the active substance or to any of the excipients. Patients in a severely immunocompromised state. Severe active infection until resolution. Known active malignancy.
Warnings/Precautions: *Injection-related reactions:* Patients should be informed that injection-related reactions (systemic) could occur, generally within 24 hours and predominantly following the first injection. From clinical studies the most frequently reported symptoms include fever, headache, myalgia, chills and fatigue. Injection-related reactions can be managed with symptomatic treatment, use of premedication is not required. Injection site reaction (local) symptoms observed in clinical studies included erythema, swelling, itching and pain. *Infections:* It is recommended to evaluate the patient's immune status prior to initiating therapy. Based on its mode of action and available clinical experience, ofatumumab has the potential for an increased risk of infections. Administration should be delayed in patients with an active infection until the infection is resolved. Since John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML) has been observed in patients treated with anti-CD20 antibodies, other MS therapies, and ofatumumab at substantially higher doses in oncology indications, physicians should be vigilant for medical history of PML and for any clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, treatment with ofatumumab should be suspended until PML has been excluded. Hepatitis B reactivation has occurred in patients treated with anti-CD20 antibodies. Patients with active hepatitis B disease should not be treated with ofatumumab. HBV screening should be performed in all patients before initiation of treatment. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment. Patients in a severely immunocompromised state must not be treated until the condition resolves. It is not recommended to use other immunosuppressants concomitantly with ofatumumab except corticosteroids for symptomatic treatment of relapses. *Vaccinations:* All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to initiation of ofatumumab for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ofatumumab for inactivated vaccines. Ofatumumab may interfere with the effectiveness of inactivated vaccines. The safety of immunisation with live or live-attenuated vaccines following ofatumumab therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion. In infants of mothers treated with ofatumumab during pregnancy live or live-attenuated vaccines should not be administered before the recovery of B-cell counts has been confirmed. Depletion of B cells in these infants may increase the risks from live or live-attenuated vaccines. Inactivated vaccines may be administered as indicated prior to recovery from B-cell depletion.
Interactions: No interaction studies have been performed, as no interactions are expected via cytochrome P450 enzymes, other metabolising enzymes or transporters. The response to vaccination could be impaired when B cells are depleted. The risk of additive immune system effects should be considered when co-administering immunosuppressive therapies with ofatumumab.
Fertility, pregnancy and lactation: Women of childbearing potential should use effective contraception while receiving ofatumumab and for 6 months after the last product administration. There is a limited amount of data from the use of ofatumumab in pregnant women. Treatment with ofatumumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. The use of ofatumumab in women during lactation has not been studied. It is unknown whether ofatumumab is excreted in human milk. There are no data on the effect of ofatumumab on human fertility.
Undesirable effects: Very common (≥1/10): upper respiratory tract infections, urinary tract infections, injection-site reactions (local), Injection-related reactions (systemic). Common (≥1/100 to <1/10): oral herpes, blood immunoglobulin M decreased.
Legal classification: POM
Marketing Authorisation (MA) number, quantities and price:
PLGB 00101/1201 - unit pack of Kesimpta 20 mg solution for injection in pre-filled pen containing 1 pre-filled pen: £1,492.50.
Date of last revision of prescribing information: April 2021
Full Prescribing Information available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.
UK | 109511 | April 2021

Adverse Event Reporting:
Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.report.novartis.com

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Kesimpta▼ is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

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Kesimpta® (ofatumumab) 20 mg injection

CONTROL WITH CONFIDENCE

Not representative of an actual patient - this image is intended to depict the brand.

KESIMPTA IS NOW LICENSED FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSING FORMS OF MULTIPLE SCLEROSIS (RMS) WITH ACTIVE DISEASE DEFINED BY CLINICAL OR IMAGING FEATURES[1]

EFFICACY PRECISION FLEXIBILITY

SUPERIOR, SUSTAINED EFFICACY
in clinical studies vs teriflunomide[1,2]

- Significant reduction in ARR of up to 59% vs teriflunomide (P<0.001) (ASCLEPIOS I: 51% (0.11 vs 0.22 in 454 and 452 patients, respectively; ARR ratio [95% CI]: 0.49 [0.37–0.65]), ASCLEPIOS II: 59% (0.10 vs 0.25 in 469 and 469 patients, respectively; ARR ratio [95% CI]: 0.42 [0.31–0.56])*[1,2]
- 9 out of 10 patients taking KESIMPTA achieved NEDA-3 in Year 2 in a post hoc analysis†[3,4]
- Across both trials, median treatment duration was 85 weeks (interquartile range: 73-97 weeks)[1,2]

TARGETED, PRECISE REGIMEN[1]

- A targeted and precisely delivered B-cell therapy‡[5,6]
- Overall generally well-tolerated safety profile with infection rates similar to teriflunomide, as demonstrated in two pivotal trials[1]

CONFIDENCE AND FLEXIBILITY
Intended for self-administration with initial healthcare professional guidance, via easy-to-use autoinjector pen[1,7]

- The first and only self-administered once-monthly (20 mg), SC, B-cell therapy

Learn more about KESIMPTA by visiting www.kesimpta.co.uk

ARR=annualized relapse rate; CDW=confirmed disability worsening; DMT=disease-modifying therapy; Gd+=gadolinium-enhancing; MRI=magnetic resonance imaging; MS=multiple sclerosis; NEDA=no evidence of disease activity; RMS=relapsing forms of multiple sclerosis; SC= subcutaneous.

Study design: KESIMPTA was studied vs teriflunomide in ASCLEPIOS I and II: two identical Phase 3, double-blind, double-dummy, active comparator-controlled, parallel-group, multicentre adaptive and flexible duration design trials in patients with RMS, approximately 40% of whom were DMT treatment naïve.[1,2]

***Primary endpoint:** relative reduction in adjusted ARR vs teriflunomide.[1]

†Post hoc analysis of KESIMPTA patients who achieved NEDA-3. Post hoc analysis of ASCLEPIOS I and ASCLEPIOS II studies included all patients from the pivotal trial full analysis set population according to the intent-to-treat principle, but patients who discontinued from the study drug prematurely for reasons other than "lack of efficacy" or "death" and had NEDA-3 before early discontinuations were excluded. The analysis occurred within the prespecified time period (i.e. 0-12 months and 12-24 months), and included patients who achieved NEDA-3, defined as no 6-month CDW, no confirmed MS relapse, no new or enlarging T2 lesions and no Gd+ T1 lesions on MRI scans.[8] 88% (8.8/10 patients) of patients taking KESIMPTA achieved NEDA-3 in months 12-24.[3,4,8]

‡As suggested by preclinical models[5,6]

Please see Prescribing Information and references on the page overleaf.

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