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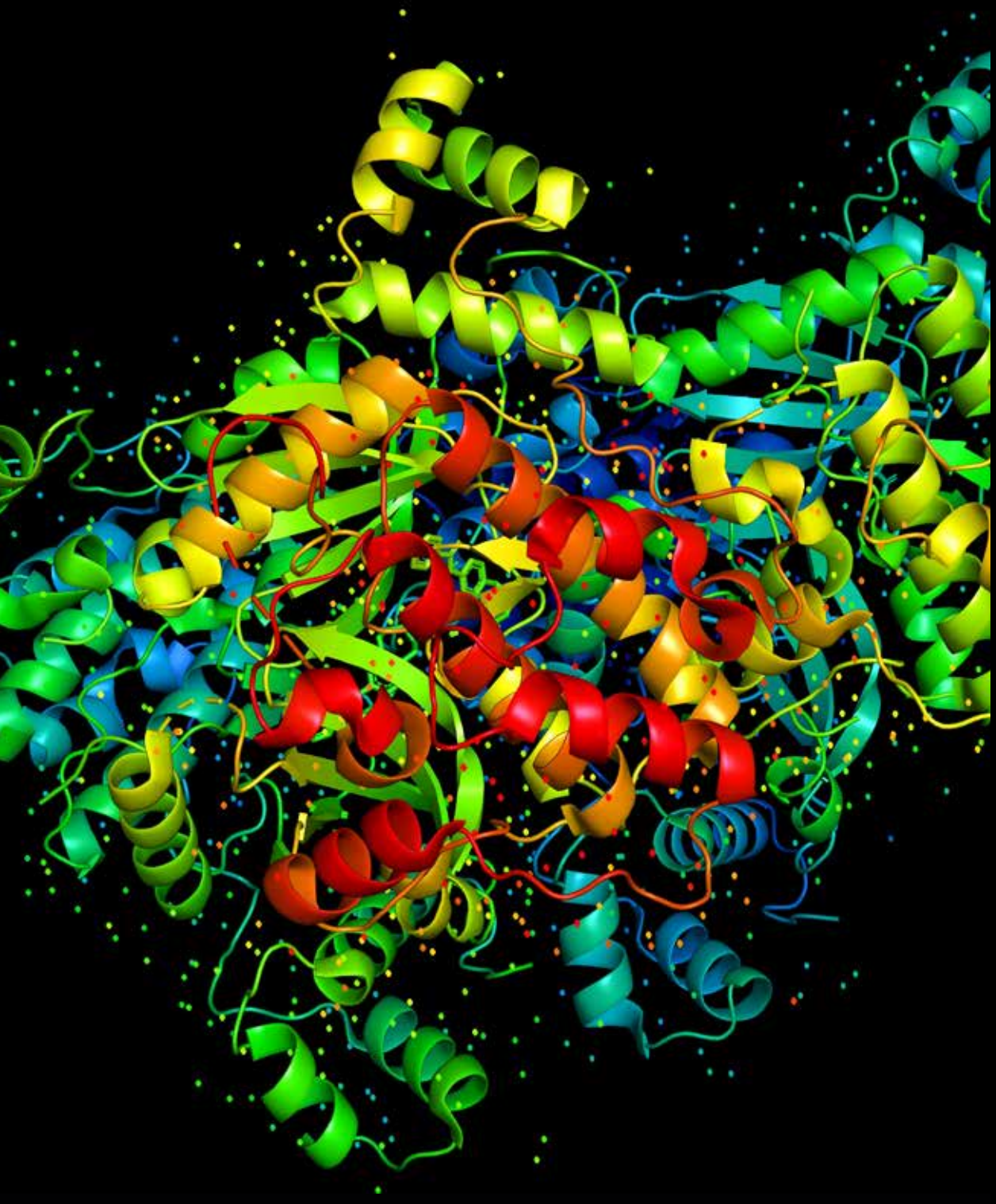

In this issue

SPOT SPMS is a medical educational campaign which was created and funded by
Novartis Pharmaceuticals UK Ltd and is intended for UK healthcare professionals only.

THE LONGER THE WAIT THE MORE DAMAGE IT CAUSES[1-3]

1 in 2 people with RRMS will progress to SPMS within 20 years.[4] Mary may only be 39, but she's been experiencing difficulty finding words and slower thinking. These cognitive symptoms can be a sign of SPMS.[5,6] And its damage can be irreversible, making an early diagnosis essential.[1,7]

SPOT SPMS.
SLOW THE BURN.

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UK | March 2022 | 196257 RRMS=relapsing remitting MS; SPMS=secondary progressive MS

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REGULARS

Cover picture *shows the structure of the protein molecule, tumour marker glioblastoma.*

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Ann Donnelly, Co-Editor.

When handing over the love of this journal to me, Professor Barker described a journal which would be filled with clinically relevant information. The scenario he envisaged was that of a busy clinician with a 'DNA' in clinic, with an unexpected 15 minute window. This journal aims to pack in articles which will inform your practice and these are designed to optimise that unexpected gift of time.

We aim to achieve this with every article, and this issue is no different, packed with information which could enhance and change your practice.

Our new movement disorders editor, Dr Edward Newman, launches a series with a comprehensive overview of the clinical approach to focal dystonia, written with Sacha E Ghandi and David G Anderson.

Although COVID no longer dominates our consciousness in the way it did in 2020 and 2021, we are still learning more about long term sequelae, Dr Manoj Sivan, Joanna Corrado and Prof Christopher Mathias give us a detailed overview of a potential home-based protocol designed to evaluate neuro-cardiovascular dysfunction in this context.

A protocol for developing a multidisciplinary pathway for functional neurological diseases is explored in detail, and with great clarity, by Dr Leo Russell et al at Exeter, and hopes to provide a replicable model for multiple other centres.

The JMS Pearce article outlining The Fatal illness of Oscar Wilde is absorbing food for thought, as always, returning to the idea of the neurologist as detective.

Looking at our everyday practice, Dr Heather Angus-Leppan from Royal Free London, highlights the often undertreated migraines, in the epilepsy population. A rare presentation of a common condition is discussed in the article Dominant parietal lobe ischaemic stroke presenting as alien hand syndrome by Tamara Al Bahri, Simon Bell et al at Sheffield.

Thinking more from a research perspective, the review by Síle Griffin and Fiona Griffin, University of Limerick, looks at the relationship of Vitamin D to apoptosis and cell cycle arrest in cancer cells, with regards to its potential use in the treatment of glioblastoma multiforme.

Professor Barker reviews Professor Andrew Lees' latest book – Brainspotting: Adventures in Neurology – both inspirational neurologists, and I look forward to reading this on my upcoming summer leave.

I wish you all a sunny, healthy summer and I hope you enjoy reading this on a sunlit afternoon.

Ann Donnelly, Co-Editor
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Developing a multidisciplinary pathway for functional neurological disorders in a UK National Health Service: The Exeter model

By Leo Russell, Lisa Butler, Chris Lovegrove, Colm Owens, Lisa Roberts, Phil Yates, Rachael Carrick, Annika Amoako and Chris Price.

Abstract
Functional neurological disorders remain common presentations to both outpatient and inpatient NHS services, but little consensus exists with respect to how such services and clinical pathways for patients should be structured and should function. This article sets out a model for an integrated multidisciplinary approach that takes full account of the number of specialties involved, constraint on resources and time involved, and that has functioned well in the NHS despite a pandemic.

Functional neurological disorders (FND) are amongst the most common presentations in outpatient neurology clinics [1] leading to approximately 8000 new diagnoses per year in the UK alone [2,3]. Functional neurological disorders can be similar in appearance to disorders of the brain and nervous system but occur in the absence of organic pathology [4]. They can be identified through careful neurology assessment not just through exclusion of organic conditions but through inclusion of positive signs for diagnosis [5].

Despite its ubiquity, FND is both under-recognised and under-resourced in the NHS. This has changed in recent years with increasing research into the aetiology, assessment, and treatment of FND as well as the establishment of the FND Society for the development of understanding of these conditions [3]. However, prognosis often remains variable with one study finding quality of life ratings to be poorer in some FND presentations than with comparable organic conditions [6] and another identifying that 58% of a tracked cohort of FND patients were still reporting symptoms 12 years later [7].

One of the major issues in the treatment of FND has been lack of understanding of the condition amongst healthcare professionals. A synthesis of 11 qualitative studies into the experience of healthcare professionals (HCPs) in working with FND found common uncertainty in the management of FND which frequently led to moving the patient care onto another discipline [8]. The authors observed that this typically leads to a vicious cycle whereby patients are "passed from one professional to another but without receiving clear, honest information, or effective treatment". They propose that clear clinical pathways are part of the solution to alleviate uncertainty in HCPs and improve treatment for patients with FND.

Development of the Exeter model as an integrated FND pathway

The NHS Five Year Forward View [9] sought to break down barriers in how care is provided between community and acute services, physical and mental health teams, and between health and social care. Devon Partnership NHS Trust responded to this with the development of the Integrated Psychological Medicine Approach which focused on establishing integrated pathways for long-term health conditions which might otherwise fall in the gap between physical and mental health services [10]. Existing Community Neuropsychology Services dedicated a small resource to working with functional neurological symptoms which evolved into an FND assessment and treatment service [11].

Over time this service worked in collaboration with Neurology and Rehabilitation specialities within the Royal Devon University Healthcare NHS Foundation Trust, developing shared expertise and trialling new initiatives [12]. This led to the emergence of a core group of interdisciplinary colleagues across both Trusts with an interest in improving care for people with FND. Following a regional conference in 2020 this group decided to form a virtual FND Multidisciplinary Team (MDT) to establish an integrated FND pathway across community and acute settings in physical and mental health services (See Figure 1).

The underlying principle of the Exeter model is that the assessment and treatment of FND is part of the core business of acute and community services and therefore should be integrated with coherent pathways and clear roles. The clinical input can either be delivered in parallel across professions or as profession-specific episodes depending on patient need. The multidisciplinary nature of the team overseeing this pathway has been essential in order to capture patients presenting at different parts of the system, to develop coherent care-plans that reach across stepped-care, and to disseminate the full range of expertise required to support patients and families with FND. The pathway includes a twice monthly MDT meeting to; discuss the management of complex case presentations, reflect on the functioning of the pathway, establish new practices and protocols, and to develop new initiatives for raising awareness of FND within local healthcare settings.

The complex case FND MDT acts as the focal point in establishing, maintaining and developing the pathway. The major strength of the MDT is the value of what can emerge from the dialogue between professions as well as in the specialist role that each discipline contributes to the pathway:

Neurology

Neurologists are first and foremost involved in the diagnosis of FND. However, their role extends beyond this to treatment and in particular using clinical signs to explain to patients how well their nervous systems can work with the appropriate education and support. Patients with FND frequently develop new symptoms that may concern HCPs and the neurologist can offer clear advice as to whether this is or is not consistent with FND. Following MDT discussions neurologists are in a favourable position to offer effective second opinions for colleagues and arrange clinical review (usually face to face, but also via online consultations especially during the COVID pandemic). This is both intradepartmental

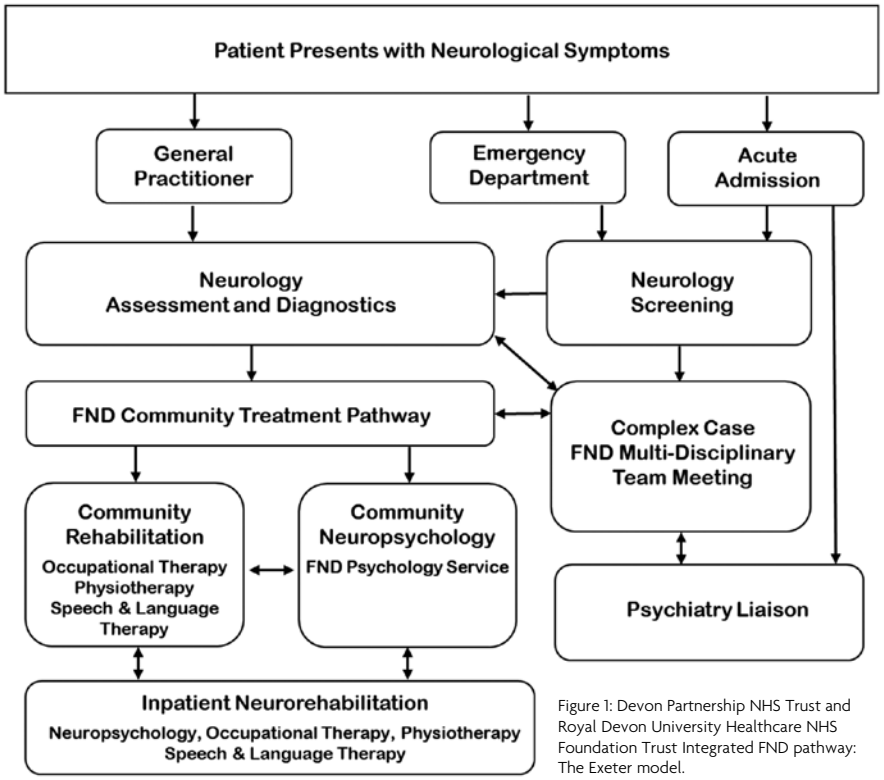

Figure 1: Devon Partnership NHS Trust and Royal Devon University Healthcare NHS Foundation Trust Integrated FND pathway: The Exeter model.

where diagnosis remains challenging and also across specialties, in particular working alongside gastroenterologists and pain specialists. Finally, the neurologist has the opportunity to learn from others within the team about aspects they may not be familiar with, e.g. personality disorders thus enlisting expertise from psychiatry colleagues or complex psychosocial backgrounds from general practitioners.

Occupational therapy

Occupational therapists work with people with FND to enable meaningful participation in activities of daily living, including work-like and leisure occupations. This can take the form of interventions such as graded task practice, fatigue/symptom management, and vocational rehabilitation. Additional interventions also utilised, if necessary, can include compensatory aids, adaptations, and splinting. These interventions are individually assessed and managed to prevent the introduction of secondary problems that may prevent the restoration of normal movement and function. An advantage of the Exeter Model is that clinicians develop the skills and experience to support colleagues to use such compensatory techniques in a way that minimises the risk to the person's recovery and avoids iatrogenic harm.

Physiotherapy

The role of the physiotherapist is pivotal at a number of levels and employs a specific skillset. Education is perhaps foremost: this involves reinforcing information from the neurologist and psychologist as well as lifestyle advice. Secondly, a more physiotherapy discrete approach should explore the effects different movement has on symptoms, encouraging normal physical activity, discouraging disadvantageous habitual postures, supporting graded activity and pragmatically yet sparingly and safely prescribing equipment. Thirdly, physiotherapists will often pick up positive signs of FND where the diagnosis is yet to be confirmed requiring effective communication with the whole team. The subtype of FND and individual circumstances of the patient will inform timing, type and intensity of intervention that a community physiotherapist offers as part of the MDT. The importance of physiotherapy expertise within the MDT has been examined in a number of studies [13,14,15,16,17].

Psychiatry liaison

Liaison psychiatrists and allied teams can usefully undertake a number of roles in the FND pathway. They are familiar with the hinterland between so called 'physical' and 'mental' healthcare delivery. Liaison psychiatrists and those other MDT colleagues working in liaison psychiatry teams can usefully undertake a number of roles in such a pathway. Firstly, they can help the wider team identify the presence of co-morbid mental disorders, or usefully exclude them. However, liaison psychiatrists do not see this as the be all and end all of their role. More subtle difficulties can be identified and a comprehensive 'bio-psycho-social' assessment can lead to a useful formulation which can be shared with the patient and the wider treating team. Liaison psychiatrists can act as 'translators' helping mental health professionals and those who work in medical environments to understand each other's language and also the realities of what services are able to achieve. Patients with functional disorders may sometimes have a background of significant psychological trauma and this can be explored sensitively and made sense of, both for the patient and the other treating professionals. Behaviours that can be experienced as challenging or anxiety provoking for non-mental health professionals can be made sense of and useful risk assessment work can be undertaken.

Psychology

The role of clinical psychology and neuropsychology in FND can include: neuropsychological testing, bio-psycho-social assessment and formulation, and a range of interventions targeting potential psychological contributors to these conditions. The potential benefits of psychological interventions for FND are supported by an emerging evidence base [18,19,20,21]. These promising outcomes have been replicated locally in a pilot evaluation of Intensive Short-term Dynamic Psychotherapy (ISTDP) offered as part of our FND pathway [22] where we also offer Eye Movement Desensitisation and Reprocessing therapy (EMDR), Acceptance and Commitment Therapy (ACT), Cognitive Analytic Therapy (CAT) and Compassion Focused Therapy (CFT). FND psychoeducation and elements of these models are also incorporated into an online format for patients where a full course of psychological therapy is not indicated or appropriate. Overall, this set of psychotherapy models provides a range of potential mechanisms for ameliorating symptoms or improving quality of life through both implicit unconscious and explicit conscious processes [23].

Speech and language therapy

Speech and language therapists work with people with functional disorders of communication (including altered fluency, voice, articulation, prosody, accent and language), swallowing and cough. They can have a role to play in diagnosis; positively identifying functional symptoms through detailed assessment and liaising with the MDT regarding next steps where required. Patients are supported to understand the specific mechanisms underlying their symptoms and due attention is given to predisposing, precipitating and perpetuating factors in collaboration with MDT colleagues as appropriate. Although there is much work to be done to develop evidence-based treatments, detailed consensus recommendations have been published [24]. Therapy can vary significantly depending on the needs of the patient but may include; bringing the focus of attention to conditions under which pathways already function well, distraction, symptom and behaviour modification, specific exercises to release muscular tension and work to promote a greater sense of calm within the body and mind. Speech and language therapists working with FND within our service also draw on principles from a

range of psychological approaches including ACT, Cognitive Behavioural Therapy (CBT) and Solution-Focused Brief Therapy.

Inpatient neurorehabilitation

There is an emerging literature on inpatient treatments and rehabilitation for FND. However, Consensus treatment guidelines have yet to be established. In this literature multidisciplinary team based interventions that include the role of physical therapy in addition to psychotherapy has increasingly been recognised [25,26,27,28]. There is preliminary evidence for the benefits of a multidisciplinary approach that utilises physiotherapy and psychological therapies such as; CBT, hypnosis and motor-retraining [27,29,30].

In relation to the specific NHS pathway described in this paper, Yates et al [31; unpublished poster presentation] carried out two retrospective studies comparing the differences in functional outcome measures of patients with FND and those with organic neurological disorders who were referred for inpatient multidisciplinary neurological rehabilitation. Both studies provided preliminary evidence that the inpatient rehabilitation pathway significantly improved the overall functioning of patients with FND over a four week period on measures of mobility; and that inpatient rehabilitation significantly reduced the complexity of need and intervention of patients. The clinical experience of the authors is that as the community FND pathway infrastructure has evolved the requirement for inpatient rehabilitation has substantially reduced.

Discussion

Operating in an emerging clinical field, we have also found it immensely helpful to extend our joint working to a wider range of colleagues and stakeholders. This has included the opportunity to work in collaboration with a local patient-led FND charity (FND FrieNDs) and with multidisciplinary colleagues across the South West in neighbouring NHS Trusts. This enables us to share and reflect on our service delivery as well as to learn from examples of good practice in the whole region.

A crucial aspect of the complex case MDT has been the ability to involve the wider network and especially general practitioners who are so often the core of effective FND care. These discussions are aimed at ensuring the right team of professionals are involved, which can lead to more productive and responsive discussions with the patient to ensure that they are getting the right care at the right time.

One area we are hoping to expand is the integration with Social Care Services. This will likely involve representation at the complex case MDT and joint work to ensure that our colleagues in Social Care are FND aware. Similar projects for raising awareness of FND have already been instigated in our local inpatient settings and are planned for our emergency department.

Conclusions

In order to address historic disparities in care for FND we found it was essential to work across professional disciplines and establish an integrated pathway of care across acute and community services. This has involved developing and sharing FND expertise, raising awareness of the condition in all settings, partnership working with our third sector colleagues, and finding time to meet regularly as a multidisciplinary group seeking better care for FND.

The Exeter model evolved from the premise that FND input should not be seen as the province of only specifically commissioned services or regional providers. People with FND and their carers deserve well-designed services that can locally meet the needs of the majority of patients through providing continuity of care and effective multidisciplinary input. We fully support the need for FND to be better resourced nationally through specific commissioning but would also encourage colleagues not to wait until funding has been secured before working together to develop pathways. Whilst we still have much to learn about effective support for people with FND, we have found the opportunity to work together on the pathway as a multidisciplinary group to be hugely enjoyable and professionally highly rewarding.

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The adapted Autonomic Profile (aAP) home-based test for the evaluation of neuro-cardiovascular autonomic dysfunction

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Abstract

Autonomic dysfunction is an increasingly recognised complication in chronic neurological conditions such as Parkinson's disease, and other medical conditions, including diabetes mellitus, chronic fatigue syndrome, postural tachycardia syndrome (PoTS) with and without Ehlers-Danlos syndrome, fibromyalgia and recently Long COVID. Despite laboratory-based tests to evaluate normal and abnormal autonomic function, there are no home-based tests to record neuro-cardiovascular autonomic responses to common stimuli in daily life that are dependent on normal functioning of the autonomic nervous system. We have developed an adapted blood pressure/heart rate Autonomic Profile (aAP) that can be used by an individual independently and repeatedly in a domiciliary setting to determine the physiological and symptomatic response to standing, food, and physical or mental (cognitive, emotional) activities. The aAP aids separating autonomic failure (often irreversible) from autonomic dysfunction. This helps the individual and attending healthcare professional understand the relationship between symptoms and common triggers in daily life and informs on self-management in debilitating conditions such as the postural tachycardia syndrome (PoTS) and Long COVID.

The autonomic nervous system (ANS) innervates the smooth muscle of all organs, including the heart, blood vessels and various glands. It is responsible for organ function and mediating involuntary internal homeostasis, to include control of blood pressure (BP), heart rate (HR) and thermoregulation. This is unlike the somatic nervous system, which largely is under volitional control. The ANS works along with the hormonal and immunological system to respond to external and internal stimuli and ensure internal equilibrium is maintained as much as possible to enable the stable functioning of various organ systems [1]. The central ANS centres are in the brainstem, hypothalamus and cerebrum; the peripheral ANS includes the sympathetic and parasympathetic nervous systems, influencing their actions on body functions via transmitters such as acetylcholine and noradrenaline.

Autonomic dysfunction (AD) can result from damage to the ANS or can be idiopathic, episodic or unexplained in some cases [1] (Table 1). Long COVID is a relatively new condition and AD is reported to be present in at least a third of individuals [2,3]. There is a considerable overlap with Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS) where one of the features can be postural tachycardia (as in PoTS) [4]. The other common symptoms of Long COVID (breathlessness, gastrointestinal symptoms and pain) have been proposed to be linked to underlying dysautonomia, which is commonly seen in post-viral syndromes [3].

Many of the tests used for ANS evaluation are based on cardiovascular reflexes triggered by performing specific provocative manoeuvres in a controlled environment. Stimuli that alter BP or HR, such as in response to standing or passive tilting on a tilt table, and in response to the Valsalva manoeuvre, isometric exercise, cutaneous cold or heat, mental arithmetic, and deep breathing activate ANS responses that can be accurately measured [5,6]. Techniques such as measuring heart rate variability (HRV), plasma noradrenaline and adrenaline levels, sudomotor testing and microneurography test specific aspects of autonomic function [6,7].

The neuro-cardiovascular autonomic responses to postural change are assessed in various ways. The active stand or NASA lean test measures HR and BP while standing for 10 min [8]. Measurements are made first while in the supine position. When upright, due to gravitational change, blood is redistributed to the lower extremities, which decreases venous return and cardiac stroke volume. Physiological compensatory responses through the ANS are activated to maintain adequate BP and HR. There initially is an immediate response with an abrupt fall in systolic and diastolic BP and a rise in HR (first 30s), with a phase of early stabilisation, after 1-2min, followed by a response to standing for more than 5min. The normal response includes a rise in HR by 10-15bpm and a slight decrease in systolic BP blood pressure, and in some a rise in diastolic BP by 10mmHg is normal [8,9]. A systolic BP fall of more than 20mmHg or more than 10mmHg for diastolic BP or a rise in HR of

Table 1. Classification of some autonomic conditions and common symptoms of or related to autonomic dysfunction

Cause	Conditions	Symptoms
Structural central	Multiple System Atrophy (MSA) Parkinson's Disease (PD) Acquired Brain Injury (ABI) Spinal Cord Injury	*Cardiovascular:* Orthostatic hypotension, palpitations, postural tachycardia, dizziness, presyncope/syncope, facial flushing *Systemic:* Fatigue, exercise intolerance *Neurological:* Brain fog, vertigo, dizziness, headache, sleep problems *Gastrointestinal:* Xerostomia, nausea, vomiting, dysphagia, irritable bowel syndrome constipation/diarrhoea *Genitourinary:* Urgency, frequency, polyuria, impotence *Musculoskeletal*: Joint pain, muscle pain *Skin/vasomotor:* flushing, piloerection, excessive sweating, intolerance to heat/cold *Eyes:* Pupillary dilation, light sensitivity, hypolacrima
Structural peripheral	Diabetes Mellitus Autonomic Neuropathy such as due to Amyloidosis Familial Dysautonomia	
Idiopathic	Chronic Fatigue Syndrome Fibromyalgia Autonomic Mediated Syncope (AMS) Postural Tachycardia Syndrome (PoTS) Irritable Bowel Syndrome Long COVID	

more than 30bpm (or 40/min in 12-19 yr olds) is considered abnormal [5-9].

The Head-Up Tilt (HUT) measures changes in BP and HR during and after passive head-up tilting to 60 degrees on a motorised table [10,11]. The acute fluctuations seen in the active stand-up test are not observed in this test, and it is a predominantly neuro-cardiovascular autonomic response without the influence of the pumping action of leg muscles. To ascertain the responses to food and physical exertion when upright, the head-up tilt test is combined with a relevant provocative stimulus such as a balanced liquid meal or a modified exercise test [5,7].

A variety of factors in daily life can influence neuro-cardiovascular autonomic responses, including body position, emotional state, activity (physical or mental), food ingestion, medication for specific autonomic conditions [12] and associated disorders, and other non-prescribed substances. The COVID-19 pandemic emphasised the need to develop home-based testing, as assessments of even core stimuli, such as postural change, food ingestion and physical exertion were needed with inaccessibility or considerably reduced capacity for specialised autonomic testing. The key aim was to enable the subject to conduct relevant tests themselves and report back to the clinician with their findings. This additionally enabled the individual and health care professional to understand the stimuli in daily life dependent on preserved autonomic function and evaluate factors that cause fluctuating symptoms. This is particularly relevant to Long COVID, which can be characterised by a daily and weekly fluctuation of symptoms.

Aims

To describe the adapted Autonomic Profile (aAP) test, provide a case example and discuss its role in evaluating and understanding neuro-cardiovascular autonomic dysfunction, and in aiding self-management in Long COVID and other conditions that cause autonomic impairment.

Methods

The aAP protocol was initially developed by one of the authors (CJM) in the early phase of the pandemic to test patients remotely and avoid laboratory testing and travel to hospital. It was based on experience over three decades and on information in the two autonomic departments that he developed and directed (at St Mary's Hospital/Imperial College London and the Autonomic Unit at Queen Square, University College London). Pre-pandemic evaluation utilised ambulatory and programmed BP/HR recorders (as used in hypertension assessment), with additional measurements while lying and standing, and to food and physical exertion [13,14]. This became challenging during the pandemic as the patients needed to travel to the centre to collect the recorders and there was uncertainty about equipment sterilising procedures to avoid virus transmission. The home adapted autonomic protocol was devised to overcome these issues and was further refined by authors MS and JC for particular use in Long COVID patients. It has gone through several iterative cycles of development using feedback from physicians, therapists, researchers and especially patients who now utilise the aAP to aid diagnosis and management.

The aAP protocol

The test involves measuring BP and HR at times as outlined below while at home, with a personal arm cuff (and not wrist), BP/HR monitor as recommended by the British Heart Foundation (giftshop.bhf.org.uk), whose website lists validated models. An example is Omron, also approved by the British Hypertension Society. The recordings provide information on neuro-cardiovascular autonomic responses to key activities in daily life such as postural change, and before and after food and exertion. Experience over the decades indicates that this protocol, even before the pandemic (from ambulatory BP/HR recorders) provided adequate data to exclude autonomic failure and dysfunction and aid initial autonomic diagnosis and guidance on treatment. The advantage with the aAP is that it can be repeated on a 'typical' or 'atypical' day and objectively can assess the response to intervention, be it non-pharmacological or pharmacological.

Unlike other standardised tests, there is no need to abstain from caffeine, nicotine, alcohol or medications for this test, as the purpose is to test in their daily life the reaction to common stimuli and record normal (or abnormal) autonomic responses to these stimuli.

To complete the aAP, time, position, BP, HR, and key symptoms in brief (such as dizziness), are recorded on the accompanying aAP diary sheet. This is of particular importance in autonomic conditions and differs substantially from BP/HR recordings commonly used for hypertension. Recordings should be taken on waking, after meals, after exertion and before sleep, with measurements taken as outlined below:

- **Waking** – The BP/HR is recorded after lying down, then after 3 minutes of sitting, and then after 3 minutes of standing.
- **Food/liquid intake** – Recordings 3-5 minutes after food ingestion at main meals (breakfast, lunch or dinner), lying down first, and then after 3 minutes of standing. A note is made of food and drink consumed (including alcohol).
- **Activity** – BP/HR recordings 3-5 minutes after any activity (physical, cognitive or emotional) morning and afternoon, separated from meals. Physical activity will be listed and individually differ and can be 5 minutes of walking, or going up and down a flight of stairs. Emotional activity may be watching an exciting sporting match or film. Cognitive activity may be 5 minutes working out a crossword puzzle. The subject should include at least one form of physical exertion if possible. Discussion with the clinical team will help determine the form of exercise or exertion that may be most appropriate.

In those more severely incapacitated and disabled they can substitute sitting for standing, especially if after exertion or food. If the patient wishes they can add any additional activities which cause or worsen symptoms, and which can be recorded with time, event/activity and position (lying, sitting, standing).

The patient ideally needs to choose a day when they can complete all the measurements. The intent is to provide relevant autonomic information during a standard day with usual activities so that no change in schedule is needed. The aAP can be repeated on another day if needed for comparison after adjusting for the triggers and assessing the effectiveness of any interventions.

The subject will need to be still while BP and

The adapted BP/HR Autonomic Profile (aAP) diary sheet

Participant Initials **Date**

* **Food and fluid intake** – please briefly state what food or drink, including alcohol, was consumed. For e.g, 08:00 water, muesli, yoghurt
* **Activity** (can be physical, cognitive or emotional) – please state the activity and for how long. For e.g., 09:00 washing dishes and cleaning kitchen for 10 min

Enter time e.g., 08:00	Position/Activity	Blood Pressure e.g., 120/80	Heart Rate e.g., 76	Symptoms e.g, felt dizzy, headache, etc.
EARLY MORNING (ON WAKING) Enter time:				
	Lying			
	After 3 min sitting			
	After 3 min standing			
BREAKFAST Time: Details of food and fluid*:				
	Lying			
	After 3 min standing			
ACTIVITY/ EXERTION Time: Details of activity*:				
	Before exertion			
	After 3 min exertion			
LUNCH Time: Details of food and fluid*:				
	Lying			
	After 3 min standing			
ACTIVITY Time: Details of activity*:				
	Before exertion			
	After 3 min exertion			
DINNER Time: Details of food and fluid*:				
	Lying			
	After 3 min standing			
BEFORE SLEEPING (IN BED)				
	Lying in usual sleeping position (as with pillows)			

Note: Measure sitting BP/HR if you find it difficult to stand.

Please record any other type of activity that you would like to tell us about and is not listed above, with time & position.

Enter time e.g., 08:00	Position/Activity	Blood Pressure e.g., 120/80	Heart Rate e.g., 76	Symptoms e.g, felt dizzy, headache, etc.

Box 2. Case example

A 51-year-old school teacher tested positive for COVID in September 2020. Her acute symptoms resolved but after 6 months she had ongoing breathlessness, fatigue, palpitations, dizziness, and a feeling of "butterflies" in the stomach. 24-hour ambulatory ECG demonstrated sinus tachycardia with a maximal HR of 154bpm.

She returned to work in April 2021 but with workplace modifications. Soon after her return she noticed worsening of symptoms on standing including dizziness and palpitations. Her smartwatch captured significant tachycardia and bradycardia episodes 148 and 35 respectively. A 70-degree 40-minute passive head-up tilt in Jan 2022 was inconclusive with HR increasing by 27bpm and no change in BP, with no typical symptoms reported except for transient dizziness. Provocative tests (such as food/exertion) were not carried out.

She completed an aAP in Feb 2022 which did not show significant BP changes but with certain stimuli, as indicated below, HR rose substantially fulfilling the criteria for PoTS on two occasions.

On walking, HR increased by 28bpm after 3 min standing when she was dizzy.
After lunch (ham sandwich and diet coke), HR increased by 27bpm after 3 min standing with headache.
After mild physical exertion (putting away washed clothes, up and down the stairs twice), HR increased by 34bpm after 3 min of standing (after exertion) and she was symptomatic.
After dinner (slice of toast, banana, decaf tea), HR increased by 40bpm after 3 min standing and she became symptomatic feeling breathless.

The aAP in this case was useful in providing evidence of dysautonomia through postural HR changes obtained in a home setting. It indicated a specific trigger for her symptoms, food ingestion, which she was not aware of. She was advised on post-prandial triggers, and this included eating smaller portions if needed more frequently and reducing refined carbohydrates by switching to low glycaemic index foods.

You can download the aAP Diary Sheet as a word file from https://bit.ly/3vAhGYw

You can download the aAP Instruction Sheet as a PDF from https://bit.ly/3cRvx6i

Table 2. Summary of the commonly used tests to screen and diagnose dysautonomia

	aAP BP/HR	Ambulatory 24-hr BP/HR	Active stand test/ NASA lean test	Head Up Tilt (HUT)
Setting	Domiciliary mainly	Home & away - machine to be collected & returned	Clinic	Laboratory with trained personnel
Supine & Upright	Active at different times	Active	Active	Passive
Equipment needed	BP/HR Monitor & aAP diary sheet	BP/HR automated recorder	BP/HR machine and recording sheet	Specialised equipment & tilt table
Testing times/duration	Specific daytime activities and repeatable when needed	Programmed Intermittent & also self-activated	Single timepoint	Continuous BP/HR during the tilt
Response to stimuli/ activity	To standing before and after food and exertion	Not part of standard test	Only standing	To passive tilt unless further provocative tests needed
Costs	Minimal – self BP/HR monitor	Reasonable – Reusable recorder and staff for guidance	Minimal - BP/HR monitor	Substantial – Equipment/staff within hospital

HR is recorded. As some may feel dizzy or possibly faint especially when standing, they ideally should lean against a wall or even have another person present whilst performing the test when standing. They should abandon the recording and sit or lie down if symptoms get worse.

Discussion

The adapted BP/HR autonomic profile is of value in the assessment of neuro-cardiovascular autonomic dysfunction. It determines the response to various stimuli in daily life, such as postural change, food ingestion, physical activity and other activities (cognitive and emotive) that can affect such individuals. It determines if orthostatic hypotension, a marker of conditions causing autonomic damage and failure (Table 1) is present, or can be excluded. It can confirm autonomic dysfunction in Long COVID and PoTS. It helps both the healthcare professional and the individual confirm which stimuli trigger autonomic dysfunction and provides a basis for rational management. Depending on the BP and HR responses this could include adjusting the amount of food intake and limiting or changing physical exertion, which are additional stimuli that can initiate or amplify autonomic dysfunction. Importantly this can be performed in a home setting independently by the subject, and repeated when needed or if there are lifestyle or medication changes, with positive and practical interaction with the healthcare professional. This avoids the dependence on evaluation in a controlled environment, such as an autonomic laboratory. The latter is important at times for diagnosis but has limitations in the number who can be assessed and its relevance to the individual in daily life.

The aAP thresholds to confirm orthostatic hypotension and postural tachycardia (as in PoTS) remain as previously established, with the former a common finding in autonomic damage/failure and the latter in conditions where there may be no apparent structural damage, such as in Long COVID and PoTS. In Long COVID it appears commonly and with fluctuant symptoms, which often are related to specific stimuli in daily life. The aAP provides both subjective and objective evaluation of the physiological and symptom variation with common stimuli. This approach also may explain Post-Exertion Malaise (PEM) or Post-Exertional Symptom Exacerbation (PESE), both described in Long COVID which can be triggered by various activities (physical, cognitive or emotional). It may be as proposed that the immunological responses to exertion in Long COVID can worsen AD and contribute to relapse [3].

In summary, given the large number with Long COVID (> 2 million in the UK alone) and that autonomic dysfunction needs evaluating, the BP and HR aAP is a practical means of autonomic assessment and also in determining the impact of intervention in such individuals. The benefits of this test can be further evaluated in large-scale Long Covid studies such as the NIHR-funded LOCOMOTION [15].

Using the aAP protocol

The aAP self-report paper version is free to use, and the MS Word/PDF copy is available on the ACNR website or University of Leeds website.

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Migraine in people with epilepsy: a treatable and neglected co-morbidity

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Abstract
Migraine and epilepsy account for more than 40% of neurology outpatients and are leading causes of disability [1]. They often co-exist and can be confused, because of shared clinical features. The borderlands and links between migraine and epilepsy have fascinated neurologists for centuries, and unresolved questions remain. Greater understanding of the relationship between migraine and epilepsy may give insight into shared mechanisms. It is already clear that treating co-existing migraine is an important therapeutic opportunity and may improve epilepsy [2].

Definitions

There are no specific biomarkers for epilepsy or migraine. Outpatient studies suggest the diagnosis of epilepsy is accurate in about 2/3 of cases [3], and migraine definitions are subjective. Revised definitions of epilepsy emphasise the chance of seizure recurrence, combining clinical and investigation features [4]. The International Headache Society definition aims for clarity, presenting migraine as an episodic headache lasting 4-72 hours. The definition requires two of the following: worsened by movement, unilateral, throbbing, moderate or severe; and either nausea and/or vomiting or photophobia and phonophobia [5]. This rigid definition misses much of the migraine encountered in clinical practice [6]. The distinctions between migraine and tension headache are also blurred, meaning that some migraine associated with epilepsy is mislabelled as tension headache. Migraine may recur with no headache or may simply be an aura, and pain may be in the abdomen or limbs, particularly in children [6,7]. Earlier definitions of migraine were more fluid, and arguably more reflective of real life – "recurrent attacks of headache widely varied in intensity, frequency and duration...commonly unilateral in onset; are usually associated with anorexia, and sometimes with nausea and vomiting; and some are proceeded by, or associated with, conspicuous sensory, motor, and mood disturbances; and are often familial" [8]. A key feature of migraine is hypersensitivity to sensory stimuli between as well as during episodes. There may be autonomic, motor, cognitive, psychic and sensory features as well as the headache [6].

Shared clinical features

Similarities between migraine and epilepsy in triggers, prodrome, aura, features of the ictus, and treatment demand careful analysis to avoid confusion.

Triggers

Alcohol withdrawal is a trigger for an estimated one-fifth of seizures, usually occurring 6-12 hours after imbibing (usually >7 U) and predominantly in genetic generalised epilepsy [9]. Alcohol-induced migraine (veisalgia or "hangovers") as well as acute sensitivity, particularly for red wine, are well recognised in migraineurs [10]. For migraine and epilepsy, sleep and food deprivation, as well as stress and relaxation may be individual triggers. With regard to visual stimuli, photophobia is a feature in 80% of people with migraine in at least some attacks [6]. In epilepsy only 5% of patients have photosensitivity or photoconvulsive seizures [11].

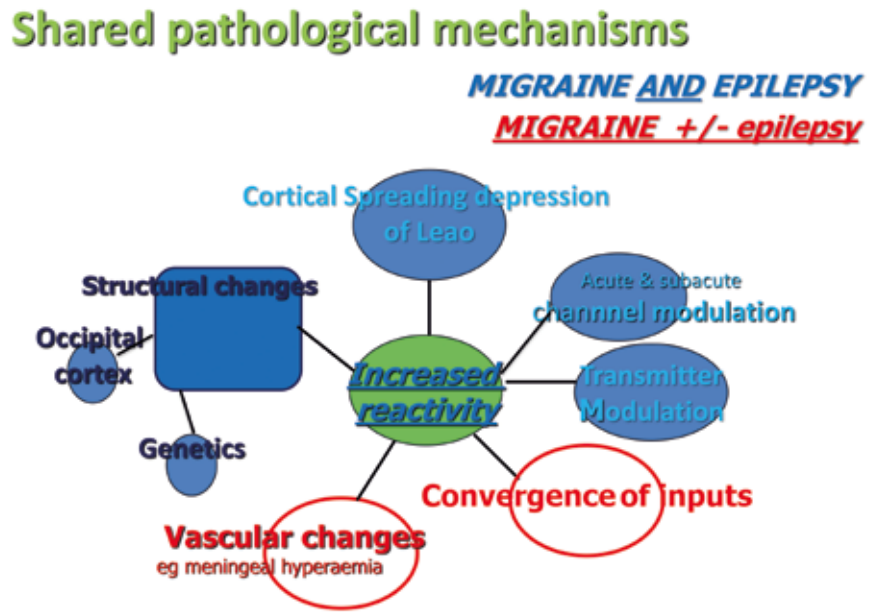
Prodrome

30-90% of people with migraine have a prodrome [12] manifestating heightened sensitivity to sensory stimuli. 6-40% (average 30%) of people with epilepsy report a prodrome, including heightened sensitivity, changes in cognition, mood or appetite, and a migraine headache in 8% [13].

Aura

Migraine aura may occur without a headache, or before, during or after one, and may be positive (such as tingling) or negative (for example hemiplegia) [6]. In epilepsy, aura (now denoted focal aware seizures) are usually positive phenomena and occur as the seizure manifestation or at seizure onset. Some aura features are similar – this is particularly important for visual, gustatory and olfactory sensations. Duration and evolution is the most important distinction – epileptic aura are usually brief with sudden onset and offset, migraine aura usually evolve and recede, lasting many minutes [6,14].

Elementary visual hallucinations are the most common migraine aura – usually linear, monochrome, 5-30 minutes duration, with gradual onset and offset [14]. They are usually distinguished from the occipital epilepsy aura, characteristically less than 2 minutes duration, rapid in onset and offset, coloured and circular [14]. Complex visual hallucinations are rare in both migraine and epilepsy and alternative diagnoses should always be considered [6,14]. Olfactory hallucinations, usually brief and unpleasant, occur in 1-66% of those with temporal lobe epilepsy [15]. They also happen in migraine, lasting between 5 minutes and 24 hours, and may be misdiagnosed as epilepsy [16]. Similarly, brief, unpleasant elementary gustatory hallucinations are well docu-



The figure models shared pathological mechanisms for migraine and epilepsy. Blue represents shared mechanisms of migraine and epilepsy. Red represents mechanisms unique to migraine.

Table I: Differentiating auras in migraine and epilepsy

Differentiating auras in migraine and epilepsy		
	Migraine	Epilepsy
Onset	Gradual – minutes	Sudden
Offset	Gradual – minutes	Sudden
Duration	Minutes to hours	Seconds to minutes
Relation to ictus	Before, during, after OR without headache	Before unaware seizure OR without unaware seizure
Allodynia	Common	Never
Visual aura	Common linear, monochrome	Rare, circular, coloured

mented in temporal lobe epilepsy but also occur in migraine. Elementary auditory hallucinations (tinnitus) are a frequent migraine aura [6]. Vestibular hallucinations (vertigo or disequilibrium) occur in 30-50% of people with migraine [17], typically lasting minutes or hours. The frequency of auditory and vestibular hallucinations in epilepsy is uncertain.

Autonomic features occur in more than 80% of migraine [5-7], usually lasting for hours, most commonly vomiting, pallor or sweating. In epilepsy they are uncommon, except in childhood occipital epilepsy and temporal lobe epilepsies. A brief epigastric aura occurs in up to 27% of people with temporal lobe epilepsy [18].

Somatosensory aura, usually tingling, is frequent in migraine. As clinical examination is normal it is often misdiagnosed as functional [6]. In migraine, head pain is present during at least some episodes in most cases. Variants include abdominal migraine or limb pain (periodic syndromes), particularly in children; but in 1-2% of adult migraine sufferers [19,20]. Ictal pain is reported in <3% of seizures [21,22], usually parietal or temporal lobe onset and most common with head, abdominal or limb pain reported, of duration from seconds to 30 minutes, and variable intensity [21]. Allodynia is a key distinguishing feature as it is not present with epilepsy, but is present in 40-60% of people with migraine [23].

Prevalence

Overall population incidence of migraine is 10%, but 50-80% in neurologists and headache specialists [24], at least partly due to heightened awareness. Migraine is primary, with a family history in about 70% [5]. The epilepsies are a collection of different conditions, occurring in 1% of the population, with established aetiology in about half, and genetic factors increasingly recognised [25]. Migraine is more common in people with epilepsy (and vice versa), estimated as 8-33% in unselected epilepsy populations with variable study design making meta-analysis problematic [2,26] and higher in those with catamenial epilepsy and migraine with aura [2]. Incidence of migraine varies with epilepsy subtype, occurring in 75% of people with occipital epilepsy [14].

Peri-ictal headache & interaction with epilepsy

There is no evidence that migraine causes epilepsy or vice versa [27] but peri-ictal headache is common and undertreated. Migraine may precede or follow a seizure, again arguing against a causal link. Migralepsy (or migraine-triggered seizures, the newer but clumsier term) [5], is described as classic visual aura followed by a seizure occurring within an hour of the aura [28]. Although controversial, it has been demonstrated electrographically in a few cases, and described convincingly in others. Marks and Ehrenberg [2] recorded the entire sequence from migraine aura to partial seizure in two patients with distinctive changes on the EEG during the migraine aura preceding the onset of an electrographic seizure. In five other patients, periodic lateralised epileptiform discharges were recorded in close temporal relation to their migraine attacks. Childhood occipital epilepsies have migrainous features at onset, and arguably represent a form of migralepsy [14]. Complicating interpretation, EEG changes occur in up to 43% of migraineurs (usually non-specific delta and theta waves, but occasionally spike-and-wave) [29]. This highlights the hazards of requesting an EEG in people investigated for syncope with co-existing migraine.

Ictal headaches are rarely described – hemicrania epileptica and epileptic headache are defined by epileptiform EEG changes [30], and as EEG is rarely recorded during migraines, the exact incidence is unknown.

Postictal headache is reported in 31-56% of patients after a tonic-clonic seizure but not after absence seizures [31,32]. 50-70% of sufferers have interictal migraine and 6% have pre-ictal headache. These headaches usually fulfil criteria for migraine [31].

Treatment of peri-ictal and inter-ictal migraine

Treating migraine in people with co-existent epilepsy and migraine potentially improves both conditions. In 6/79 (8%) of patients with refractory epilepsy, adding anti-migraine treatment to ASMs improved seizure control [2].

There are no randomised controlled trials specifically investigating treatment of migraine associated epilepsy. Some antiseizure medications (ASMs) work for both migraine and epilepsy. Topiramate and valproate have class I evidence for efficacy in both conditions [33]. Of other drugs with efficacy in epilepsy, levetiracetam, lamotrigine, gabapentin and pregabalin have also been trialled for migraine but without conclusive evidence of efficacy [34]. Most of the standard migraine treatments are suitable for people with epilepsy, and considerations are summarised in the Table 2. Whether to try to treat both conditions with a single medication, or separately, is a matter of individual clinical judgement tailored to the individual's lifestyle, co-morbidities and treatment preferences.

Table 2: Treating migraine in people with epilepsy

Medication	Efficacy in migraine	Considerations if used in people with epilepsy & migraine
Acute treatments		
Aspirin	High	Potential for metabolic acidosis with ZON, TOP & ACZ
Triptans	High	Nil known interactions
2nd generation Gepants	Less effective than triptans	Gepant levels reduced by phenytoin, phenobarbitone, less reported cardiovascular adverse events than triptans
Preventive treatments		
Beta blockers	High	No significant interactions
Tricyclic antidepressants	High	Small risk of increased seizures
Angiotension blockers	Moderate-high	No significant interactions
Aspirin	High	Potential for metabolic acidosis with ZON, TOP & ACZ
CGRP antagonists	High	No reported pharmacokinetic interactions
Botulinum toxin	Moderate-high	No significant interactions
External stimulators	Low	No significant interaction
Neuromodulation	Low	No significant interaction
ASMs repurposed as migraine preventive treatments		
Topiramate	High	Not for PPC
Valproate	High	Not for PPC
Gabapentin	Very low – same efficacy as placebo	Not effective for migraine
Pregabalin	Very low	Not effective for migraine
Levetiracetam	Low	Not effective for migraine
Lamotrigine	Low – same efficacy as placebo at 12/52	Not effective for migraine
Carbamazepine	Low	Not effective for migraine

ASMs = Anti-seizure medications, ZON = Zonisamide, TOP = Topiramate, ACZ = Acetazolamide, PPC = People potentially conceiving

Shared mechanisms

Links between migraine and epilepsy are indirect. Shared pathological factors include structural changes in the occipital cortex, genetic changes particularly channelopathies, cortical spreading depression of Leão [14,32] and acute and sub-acute channel and transmitter modulation [14]. Specific transmitter changes in the occipital cortex may have a role, with increased glutamate-to-glutamine ratio reported in women with migraine, and high neuron-to-astrocyte ratio, with these neurons containing the high glutamate-to-glutamine ratio [14,32]. Astrocytes, important in the reversal of the changes of cortical spreading depression are less in occipital cortex [14]. Trauma may cause epilepsy through glutamate receptor activation, excitotoxicity and hypersynchrony, changes which can also trigger migraine [14]. Rare monogenic channel defects produce both migraine and epilepsy [35]. Convergence of inputs and vascular changes, particularly meningeal hyperaemia are important mechanisms in migraine, little studied in epilepsy [36,37]. Analysis of the mechanisms of the two ASMs with proven efficacy in migraine does not resolve pathogenesis, due to their multiple mechanisms of activity. Topiramate changes GABA, AMPA, sodium channels and calcium channels, and sodium valproate increases GABA, enhances GABA response, increases potassium conductance and reduces neurogenic inflammation [33].

Conclusions

Careful clinical assessment usually allows differentiation of the shared features of migraine and epilepsy. Migraine is a common co-morbidity for people with epilepsy, occurring in more than 20% of people with epilepsy overall, and 75% in people with occipital lobe epilepsy [14]. It is most commonly post-ictal, but may also be prodromal, pre-ictal, or ictal. Most migraine therapy can be used safely in people with epilepsy. Pro-active treatment of co-morbid migraine reduces an unnecessary burden for people with epilepsy, and may directly improve their epilepsy [2].

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Vitamin D: A complementary nutritional therapy for treatment of glioblastoma?

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Abstract
The active vitamin D hormone, 1,25-dihydroxyvitamin D_3, is well established to inhibit cellular proliferation and induce differentiation in several cell types of the central nervous system. Indeed, a myriad of studies demonstrate the important role 1,25-dihydroxyvitamin D_3 plays in maintaining a healthy brain and nervous system. This mini review will briefly summarise in vitro, in vivo, and epidemiological evidence related to the anti-proliferative and anti-cancer activities of vitamin D in hyperproliferative disorders like brain cancer. Here, we focus on the clinical application of 1,25-dihydroxyvitamin D_3 and vitamin D analogues (synthetic vitamin D-like compounds) in glioblastoma treatment and discuss their potential as efficacious and tolerable adjunct therapeutic agents for patients diagnosed with this aggressive form of brain tumour.

Glioblastoma accounts for approximately 50% of all brain tumours in adults and is considered incurable due to its heterogeneity and complex pathogenesis [1]. Despite advancement of modern therapies against glioblastoma, it remains a deadly disease with poor prognosis and significantly impacts on quality of life throughout the disease course [2]. Median patient survival rates range between 14-16 months following diagnosis, and a five-year survival rate of 9.8% in patients [1], resulting in a critical public health issue. Indeed, treatment of glioblastoma remains the most challenging task in clinical oncology. Current therapeutic management involves maximal surgical resection of the tumour along with radiation and concomitant adjuvant temozolomide (TMZ) therapy [3]. However, glioblastoma has a poor response to current conventional chemotherapeutics due to varying side effects along with a relatively short half-life of TMZ-based chemotherapy (1.8 hours) [1]. 1,25-Dihydroxyvitamin D_3 has emerged as a target of interest to be co-administered with different brain cancer treatments due its anti-proliferative and pro-differentiation effects in the CNS, including gliomas, and ability to cross the blood-brain-barrier [4-6]. Indeed, early studies conducted on rat glioma demonstrated that such cells respond to 1,25-dihydroxyvitamin D_3 [7]. Thus, there are long-standing academic and patient-specific interests in vitamin D supplementation as a possible concomitant therapy to counteract tumour growth or reduce cancer risk.

Vitamin D and Vitamin D Analogues: Regulators of cell proliferation

Multiple in vitro studies have shown that 1,25-dihydroxyvitamin D_3 promotes a proliferation-to-differentiation switch in several cell types by promoting progression through the cell cycle and subsequently driving the cells to a more differentiated phenotype [5,8]. This has been reported to occur via regulation of cell cycle protein and senescence markers [2]. The mechanisms underpinning these anti-proliferative properties elicited by 1,25-dihydroxyvitamin D_3 differ across different cell types and cell lines derived from the same type of cancer [2]. Some of the known effects induced by 1,25-dihydroxyvitamin D_3 are mediated through the nuclear vitamin D receptor (VDR), a transcription factor belonging to the superfamily of nuclear receptors for steroid hormones [9]. VDR is almost ubiquitously expressed throughout the human body, including the CNS, and functions by regulating over 500 genes by the ligated VDR protein's binding to vitamin D response elements, subsequently leading to gene activation and suppression [10]. Notably, increased levels of VDR expression have been reported in different cancer types, particularly in glioblastoma versus lower-grade gliomas [11]. More recent evidence also reports overexpression of a new oncogene, MED12, in glioblastoma patients which identifies as an important mediator of VDR signalling and an attractive target for future studies in the context of glioblastoma pathogenesis [12].

It is important to note that preclinical data reveal that the levels of 1,25-dihydroxyvitamin D_3 needed to significantly suppress cellular proliferation is greater than normal physio-

logical levels [13]. For example, the most active metabolite of the 1,25-dihydroxyvitamin D_3 hormone, calcitriol, exerts therapeutic effects at concentrations of 10^{-8} to 10^{-4} M [13], thus leading to serious side effects such as hypercalcaemia and possible complications during cancer treatment [2]. This has therefore led to the production of safer alternative synthetic analogues of 1,25-dihydroxyvitamin D_3, including tacalcitol, calcipotriol, ML-344, EM1, CB1093, EB1089, KH1060, MC903 and MC1288, all of which have proved to be able to induce anti-tumour activity in glioblastoma without giving rise to severe hypercalcemic side effects and bioavailability issues [1]. Importantly, synthetic vitamin D analogues have been shown to interact with the VDR [14], and are also reported to suppress cellular proliferation and viability in different cancer cells [15-17]. Evidence reported by Salomón et al. showed that glioblastoma associated with VDR expression is linked with a better long-term survival of patients, thus supporting a role for VDR in glioma progression [18]. The group also investigated the role of VDR in cellular survival, migration and/or invasion (i.e., important processes in glioma progression) using human glioblastoma T98G cells, a cell line that does express VDR. They found that silencing VDR in the T98G cell line significantly increased cellular survival, whereas supplementation with calcitriol (the active 1,25-dihydroxyvitamin D_3 hormone) subsequently increased VDR mRNA and protein levels and suppressed glioma cell survival [18]. Similarly, the ability of 1,25-dihydroxyvitamin D_3 to suppress migration and proliferation in the T98G human glioblastoma cells was reported by Emanuelsson et al. [19]. The group also demonstrated significant suppression of proliferation and migration of T98G cells by both calcipotriol and tacalcitol, with stronger effects observed with tacalcitol [19].

Vitamin D and Vitamin D Analogues: Modulators of glioma risk and progression

Clinicians commonly use circulating vitamin D (25-hydroxyvitamin D_3) to determine the index of vitamin D status in the body [20]. As defined by the Endocrine Society's Practice Guidelines of Vitamin D, circulating 25-hydroxyvitamin D_3 serum level in humans lower than 20ng/ml, from 20 to 30ng/ml, and higher than 30ng/ml are indicative of a deficiency, a relative insufficiency, and a sufficiency of vitamin D, respectively [21]. Interestingly, some epidemiological studies and clinical observations indicate a connection between vitamin D deficiency or low circulating 25-hydroxyvitamin D_3 serum levels (due to limited sun exposure essential to convert cholecalciferol to Vitamin D and/or poor dietary intake) to an increased risk of developing gliomas and put forth a potential application of this vitamin as a biomarker in glioblastoma prevention or earlier prognosis, reviewed in [16,22]. Epidemiological data also suggest a higher risk of brain tumours in adults, to winter births [16] and comparative studies on blood bank specimens correlate higher prediagnosis serum 25-hydroxyvitamin D_3 levels to lower risk of glioblastoma in men over age 56 years [23]. Glioblastoma patients with 25-hydroxyvitamin D_3 serum levels greater than 30ng/mL prior to initiation of chemotherapy and radiation demonstrate longer overall survival [16], highlighting the strong potential of supplemental vitamin D to reduce mortality in patients compared to non-users. Patients supplementing vitamin D following diagnosis of glioblastoma have also been reported to have a survival advantage [24].

Data from preclinical studies have highlighted the potential of combining the synergistic effects of 1,25-dihydroxyvitamin D_3 effects with other therapeutic options for glioblastoma. For example, one study showed that TMZ and vitamin D co-administration significantly inhibited tumour progression, concomitantly enhancing survival duration in rat glioblastoma orthotopic xenograft models, when compared to TMZ treatment alone [25]. However, despite extensive in vitro and animal studies in this field, limited small-scale clinical trials have been conducted to thoroughly evaluate the safety and efficacy of concomitant treatment with vitamin D or vitamin D on its own in the treatment of glioblastoma. A phase II clinical trial conducted by Trouillas et al., investigated adjunct alfacalcidiol (vitamin D analogue) administration in synergy with classical surgery–radiotherapy–chemotherapy treatments during treatment for malignant glioblastoma. The study reported safety of the supplementation in addition to induction of a progressive and durable regression of the tumour in some patients [26]. Ongoing phase I/II clinical trials are currently underway to determine the combinatorial effects of calcitriol with other chemotherapeutic agents on glioma and other brain tumours. In a phase I/II clinical trial, the efficacy and toxicity of long-term high-dose 1,25-dihydroxyvitamin D_3 (daily dose of 4000 IU) with concurrent chemoradiotherapy containing TMZ followed by adjuvant chemotherapy containing TMZ is being investigated in newly diagnosed glioblastoma patients (ClinicalTrials.gov Identifier: NCT01181193). In another phase 1 trial, the effectiveness, and maximum tolerated doses of subcutaneous and/or oral calcitriol combined with intravenous carboplatin is being investigated in the treatment of advanced solid brain tumours (ClinicalTrials.gov Identifier: NCT00008086).

Conclusion and future perspectives

Findings based on different mouse, rodent, and human glioma cell lines report that 1,25-dihydroxyvitamin D_3 and vitamin D analogues may promote cell cycle arrest, apoptosis, anti-migratory and anti-invasive effects in various types of brain cancer cells. These compounds also appear to function synergistically when combined with other cancer therapeutics for glioma. Although the preclinical and epidemiologic data are persuasive, the relevance of findings based on in vitro and preclinical studies must eventually be validated in well-designed human clinical trials to support the assertion of 1,25-dihydroxyvitamin D_3 as a complementary nutritional therapy in the treatment of glioblastoma. Furthermore, future research should also focus on the development of improved vitamin D analogues, which are efficient in low doses and safe for co-administration to glioblastoma patients whose tumours express a vitamin D-responsive receptor.

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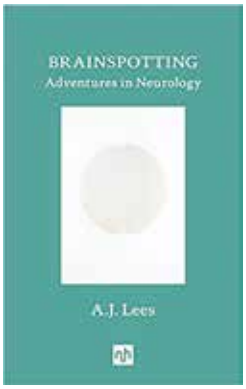
Brainspotting: Adventures in Neurology



Author: AJ Lees
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Reviewed by: Roger Barker, University of Cambridge and The Cambridge Centre for Brain Repair, UK.
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In his new book, Brainspotting, Andrew Lees takes us through his life using a series of short chapters around key events which begins with his passion for bird spotting at the age of 12 – a skill which has lain at the centre of his neurological practice. This skill of observing, recognising and linking together clinical signs and elements of behaviour is key to being able to diagnose patients with neurological diseases as well as alerting one to conditions that have yet to be described! This is something that Andrew has done spectacularly well through an illustrious career in which he has described and discovered so much including therapies for which, in some instances, he was the first volunteer!! (see Mentored by a Madman: The William Burroughs Experiment). For many of us, Andrew has been an inspiring mentor and colleague with his wealth of knowledge and openness to explore and embrace new ideas while always being so personable. This I would say suffuses this delightful book – the relationships and companionship of being a neurologist, learning not just from those that came before you but also from those after you – ensuring that you never feel that you have reached a point where you cannot learn anything new. Linked to this, as one would expect, is his keen interest in medical history which is evident everywhere in this book as he describes and discusses the origin of many well-known neurological conditions and neurologists.

This book collects together 11 separate episodes spanning his career from times in training at medical school to fond reminiscences of the old Maida Vale hospital, which used to represent the northern border of the National Hospital for Neurology at Queen Square in much the same way as Chalfont defined its western reaches. Across these episodes, we meet doctors and neurologists that have inspired him through their diagnostic skills – and quite naturally Andrew worries that these powers of observation and deduction will be left on the pages of cases solved by Sherlock Holmes rather than in the outpatient clinic where the temptation to just order tests can sometimes get in the way of clinical acumen and insight. Further to this is the remarkable breadth of skills and interests that are on display in this book. Andrew not only shows us the fascination and sophistication of clinical neurology but explores the psychiatry and psychology that is so intimately linked to it. This even extends to neuropathology and the beauty that lies on the other side of the lens which also conjures up a history of that person in life who went on to develop such a disease. All of this led to Andrew setting up the brain bank in London near the National Hospital from which so many pioneering and defining studies have come.

This book I recommend to all with an interest in neurology and especially those that practice it. For those of us that were fortunate enough to be mentored and supported by Andrew, this book brings back many happy memories as well as new insights into this remarkable neurologist. The book is packed with advice and inspiration, all of which might explain why Andrew once sent me a patient when I was on call at the National with what he correctly diagnosed as having myasthenia gravis, based on the patient's fatiguable ptosis at a dinner party he had been at the night before. For me, fatiguable ptosis at a dinner party relates to what has been consumed and the level of interest in my conversation, but for Andrew, it directed him to the neuromuscular junction. That is why Andrew is and continues to be, a remarkable neurologist, who also has that rare gift of being able to capture it in words and stories.

Queen Square Multidisciplinary Neuro-oncology Teaching Course

Location: 33 Queen Square lecture theatre 28th September 2022: Principles of Neuro-oncology & 11th January 2023: Benign and Malignant Tumours Course Director: Dr Jeremy Rees

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

Course fees:

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

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

Info: d.blundred@ucl.ac.uk

The 3rd Queen Square Movement Disorders Short Course

6-7th October 2022, Queen Square Lecture Theatre, London, UK
Course Organisers: Prof Anthony Schapira and Dr Amit Batla

On completion, participants should be able to manage patients with movement disorders in their clinical practice with updated knowledge and confidence. The teaching sessions cover all aspects of movement disorders including Parkinson's disease and atypical parkinsonism, tremor, dystonia, tics and functional movement disorders. Presentations on Deep Brain stimulation and Botulinum toxin injections.

The course is endorsed by International Parkinson and Movement Disorder Society (MDS). The Queen Square Movement Disorders Short Course has been approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 10 category 1 (external) CPD credits.

Course fees:

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

https://www.ucl.ac.uk/ion/events/2022/oct/3rd-queen-square-movement-disorders-short-course-6-7th-october-2022

Info: MDSC2019@live.ucl.ac.uk l.taib@ucl.ac.uk

Queen Square Multiple Sclerosis (MS) Course

Queen Square MS Centre – Clinical Update Course 3rd and 4th November 2022, Online Zoom webinar
Course Directors: Professor Ahmed Toosy and Dr Declan Chard

Covers key clinical issues in MS, serving as an update on this advancing field. Accessible to non-neurologists and neurologists. Lecturers have all been chosen for expertise and relevant experience in clinical practice and research.

Course fees:
GPs and Consultants – £50 for 2 days
Trainees and allied healthcare workers – £20 for 2 days
External students – £10
UCL/UCLH staff & students – free of charge
10 CPD approved credits applied for

https://www.ucl.ac.uk/ion/study/virtual-queen-square-multiple-sclerosis-ms-course-clinical-update

Info: h.ormsby@ucl.ac.uk

Stroke One Day Course: Advanced Stroke Neuroimaging

Date: 2nd November 2022, 9am - 5pm
Location: Basement lecture theatre, 33 Queen Square, London, WC1N 3AR
Faculty: Prof David Werring and Dr Sumanjit Gill

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

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

Course fee: £140

https://www.ucl.ac.uk/ion/study/stroke-one-day-course-advanced-stroke-neuroimaging

Info: m.khanom@ucl.ac.uk

Neurology 2023: leading edge neurology for the practising clinician

30th & 31st March 2023
29th March 2023: Pre course symposium: Preparing for the Speciality Certificate Exam
Course organiser: Dr Tabish Saifee

The course is designed for consultants and trainees at all levels in neurology and other neuroscience specialties, from the UK, Europe and worldwide, and aims to provide a practical update on the hospital management of neurological diseases. The focus of the course is on everyday neurological practice which will include lectures, a quiz and a CPC. The course will be didactic, but also entertaining and informative.

10 CPD points applied for with the Federation of the Royal Colleges of Physicians for the main course

Thursday and Friday Course fees:
Consultant and associate specialists – £140 for 2 days
Clinical trainees and research fellows – £80 for 2 days
UCL/UCLH Staff – £10 for 2 days
Students: – £10 for 2 days

Pre course symposium – £20 for the half day course

https://www.ucl.ac.uk/ion/neurology-2022-leading-edge-neurology-practising-clinician

Info: d.blundred@ucl.ac.uk

Movement disorders – Introduction

Over the next few editions, we will run a wide-ranging series of clinical movement disorder articles. There is a Scottish theme to the first three articles with the authors hailing from Edinburgh, Dundee and Glasgow.

In their article titled 'Functional tics, the pandemic and social media' Neil Ramsay, Vicky Marshall and Jon Stone will make sense of the upsurge in functional tics reported during the COVID-19 pandemic and discuss whether, as widely reported in the press, social media had a role in this.

In clinical neurosciences, we love using new technologies to revive old ideas and surgical thalamotomy is one of the oldest ways of managing tremor. Tom Gilbertson and Sadaquate Khan have been instrumental in the recent establishment of an MR guided focused ultrasound service at Ninewells Hospital, Dundee. In their paper, they will outline the latest evidence for the use of MR guided focused ultrasound in tremor and discuss where this treatment may go.

Recognising and confidently diagnosing focal dystonias can be challenging for the general neurologist. In this first article in our series, entitled 'A Clinical Approach to Focal Dystonias' Sacha Gandhi, Dave Anderson and I discuss the common presentations of adult-onset cranio-cervical and limb dystonias.

This movement disorder series will continue later this year with articles on pathophysiology of non-motor aspects of Parkinson's disease and other fascinating topics. I encourage you strongly to read these articles and thank you for your time.

Ed Newman, BSc(MedSci), MD, FRCP,

is ACNR's Movement Disorders Editor. He is a Consultant Neurologist at Queen Elizabeth University Hospital and Glasgow Royal Infirmary, UK. He has a specialist interest in movement disorders and Parkinson's disease. He is part of the national DBS service in Scotland and runs a Parkinson's disease telemedicine service to Western Isles. He also runs the clinical neurosciences teaching programme for University of Glasgow's Medical School.

A clinical approach to focal dystonias

By Sacha E Gandhi, David G Anderson and Ed Newman

Abstract

Dystonia is a hyperkinetic movement disorder (HMD), characterised by sustained or intermittent involuntary muscle contractions resulting in abnormal postures and/or movements [1]. Although primary dystonia has an estimated prevalence of 16 per 100,000 [2], the diagnosis may be delayed, due to its clinical heterogeneity, the lack of objective biomarkers and the potential for pseudodystonic conditions to mimic it [1,3]. We provide an overview of the classification and common subtypes of focal dystonia, focusing on the clinical phenomenology and diagnosis.

Clinical features of dystonia

Dystonia is diagnosed clinically, based upon its phenomenology. In dystonia, involuntary co-contraction of agonist and antagonist muscles gives rise to abnormal postures and movements. Dystonic movements are often stereotyped, patterned and twisting, and may be tremulous. Dystonia is often exacerbated by voluntary movement or posture and may be task-specific. Over time, however, it may manifest with less specific movements or emerge at rest. A core clinical feature of dystonia is the geste antagoniste, a so-called alleviating manoeuvre or 'sensory trick' that transiently improves the movement or posture. The term 'sensory trick' may be a misnomer. Although the exact mechanism remains elusive, it is likely that motor output plays a greater role in alleviating the dystonia than sensory input from the periphery. Other clinical hallmarks include mirror dystonia and motor overflow. Mirror dystonia describes abnormal posturing or movement elicited by activities performed by the contralateral unaffected body region. Patients with writer's cramp, for example, may exhibit a mirror dystonia of their affected hand when writing with the contralateral unaffected hand. Motor overflow occurs when involuntary muscle contractions spread from the primary site of dystonia to a contiguous unaffected body region [1]. Non-motor features of dystonia, including neuropsychiatric comorbidities, pain, impaired cognition and sleep, contribute to impaired quality of life [4]. We will use the term pseudodystonia to describe a heterogeneous group of conditions with abnormal postures and/or repetitive movements that may mimic dystonia. These conditions have phenomenological features and underlying aetiologies which are not compatible with dystonia [1].

Classification of dystonia

Classification schemes for dystonia have been proposed and refined several times since Oppenheim first described the condition in 1911. The current classification scheme categorises dystonia into two distinct axes: 1) clinical characteristics and 2) aetiology. The clinical axis incorporates age at onset (infancy, childhood, adolescence, early and late adulthood); the affected body regions (focal, segmental, multifocal and generalised); temporal pattern (static or progressive; persistent, paroxysmal, or diurnal; action-specific), and any additional associated features including other movement disorders. The second axis, aetiology, encompasses anatomical changes on imaging or pathology and the pattern of inheritance [1].

Focal dystonia refers to dystonia confined to a single body region. It almost always affects adults, and typically involves the face, neck or upper limbs. Diagnostic criteria have recently been validated for blepharospasm [5], and expert recommendations may aid in the diagnosis of laryngeal [6], cervical, oromandibular, and limb dystonia [3]. These emphasise basing the diagnosis on its positive phenomenological features, supported by the presence of a geste antagoniste. Negative features suggestive of dystonia mimics should be excluded. These include fixed postures, neuromuscular weakness, and the ability to voluntarily suppress spasms, suggestive of tics [3]. Different types of focal dystonias may co-exist. Typical combinations include cervical dystonia (CD) with writer's cramp, CD with Meige syndrome, and CD with laryngeal dystonia (LD).

Table 1: The differential diagnosis of the focal dystonias	
Differential diagnosis of the focal dystonias	
Cervical dystonia	Other hyperkinetic movement disorders – Dystonic neck tics – Functional movement disorder
	Fixed involuntary posture caused by: – Rheumatological neck disease – Trauma / orthopaedic neck disease (e.g. atlanto-axial subluxation, fractured cervical vertebrae) – Congenital torticollis – Scoliosis – Camptocormia – Neck or posterior fossa tumour – Arnold Chiari malformation – Klippel-Feil syndrome
	Weakness of the neck muscles causing or antagonising the abnormal posture: – Lower motor neuron diseases including motor neuron disease, neuromuscular junction disorders (e.g. myasthenia gravis) and myopathy
	Idiopathic drop head syndrome
	Head tilt related to a trochlear nerve palsy or vestibulopathy
Blepharospasm	Other hyperkinetic movement disorders: – Functional movement disorder of facial muscles – Eyelid tics – Bilateral hemifacial spasm
	Apraxia of eyelid opening – Evaluate for parkinsonian disorders, such as progressive supranuclear palsy – Can occur after deep brain stimulation for Parkinson's disease
	Ptosis caused by: – Neuromuscular junction disorders (e.g. myasthenia gravis), myopathies, and mitochondrial cytopathies
	Primary ocular disorders with eyelid irritation and excessive blinking
Laryngeal dystonia	Muscle tension dysphonia
	Essential vocal tremor
	Functional movement disorder
Oromandibular dystonia	Other hyperkinetic movement disorders: – Tardive dyskinesia – Jaw tics with ability to suppress the movements – Hemi-masticatory spasm – Geniospasm – Bruxism – Edentulous dyskinesia – Essential tremor involving the jaw – Parkinson's disease related jaw tremor – Functional movement disorder
	Weakness of the muscles of mastication – Lower motor neuron diseases including neuromuscular junction disorders (e.g. myasthenia gravis) and myopathy
Limb dystonia	Other hyperkinetic movement disorders: – Tics – Functional movement disorders (including chronic regional pain syndrome, CPRS)
	Stiff person syndrome spectrum disorders
	Fixed involuntary posture caused by: – Rheumatological or orthopaedic disease (e.g. Dupytren's contracture, tenosynovitis)
	Spasms related to electrolyte disturbance (e.g. hypocalcaemia, hypomagnesaemia) Upper motor neuron disease resulting in spasticity, weakness and abnormal posturing Weakness secondary to lower motor neuron disease
Adapted from Defazio et al. 2019 and Albanese et al. 2013	

Adult onset focal dystonias

Cervical dystonia

Cervical dystonia (CD), by far the most common adult onset focal dystonia (AOFD), has a predilection for Caucasian females in their fourth decade [7]. Patients often report a gradual onset neck pain, stiffness or 'pulling' sensation, followed by abnormal head and neck postures and movements. However, dystonia with an acute onset has been described and may be associated with trauma [8]. The Col-Cap concept classifies dystonia according to the position of the cervical spine (collum-type, CACOL), the position of the head (caput-type, ACAP), or both (shifts). This categorises CD into 11 distinct subtypes: torticollis, torticaput, anterocollis, anterocaput, retrocollis, retrocaput, laterocollis, laterocaput, lateral shift, forward sagittal shift and posterior sagittal shift (both retrocollis and anterocaput combined) [9]. A significant proportion of patients may have associated head tremor [7], jerking or phasic movements. The dystonia

may be exacerbated by anxiety and transiently ameliorated by a geste antagoniste, such as touching the lower face. CD is associated with psychological and functional disability, together with significant pain in up to 70% of patients [10], which may impact upon activities of daily living (ADLs) such as reading, watching television and driving.

The majority of CD is idiopathic but genetic and acquired causes are recognised. It may occur as an acute dystonic reaction or tardive syndrome, or may arise secondary to parkinsonian disorders, structural lesions, trauma or autoimmune disease [11]. Underlying focal lesions can localise to the brainstem, cerebellum, basal ganglia or cervical spinal cord [12]. CD mimics include neck tics, neck weakness from neuromuscular disease, and fixed involuntary postures secondary to rheumatological or orthopaedic disease, as illustrated in Table 1.

CD has been rarely described in patients with genetic mutations typically associated with generalised dystonias, such as DYT-TOR1A but more commonly with DYT-THAP17. Craniocervical dystonia, including isolated CD, has been reported in patients with DYT-GNAL7,13, DYT-ANO314 and CIZ115, although the role of the last two mutations in CD requires further confirmation.

Blepharospasm

Blepharospasm (BSP), one of the most common forms of AOFD, has a mean age at diagnosis of 55.7 years [16]. According to recently validated diagnostic criteria [5], blepharospasm is characterised by bilateral, synchronised and stereotyped orbicularis oculi spasms, leading to eyelid narrowing or closure. A geste antagoniste provides further support for diagnosis. If a geste antagoniste is absent, lack of suppressibility or excessive blinking may enhance diagnostic sensitivity and specificity [5]. Applying these criteria may accurately differentiate BSP from mimics, including tics, ptosis secondary to neuromuscular disease and apraxia of eyelid opening (often associated with parkinsonian disorders such as progressive supranuclear palsy) [5]. Severe BSP may render patients functionally blind, impacting upon their ability to read, watch television, independently ambulate and drive.

The pathogeneisis of BSP is multifactorial, with both environmental and genetic factors. Ocular disease, such as dry eye and keratoconjunctivitis, often precede its development, and caffeine may exert a protective effect [16-17]. Although most cases are sporadic, between 11-30% of patients with BSP disclose a family history of dystonia, lending support to an underlying genetic predisposition [17].

Laryngeal dystonia

Laryngeal dystonia (LD) is a rare task-specific focal dystonia, in which laryngeal dystonic spasms selectively impair speech. The condition may present insidiously or abruptly, often in female patients in their forties, following a period of major stress or an upper respiratory tract infection [18]. Adductor (ADLD) and abductor LD (ABLD) are the most common subtypes, although other variants have been described (mixed LD, adductor respiratory dystonia, and singer's dystonia). Speech has a strained, 'strangled' quality in ADLD, due to hyperadduction of the vocal cords, but is 'whispering' with breathy pauses in ABLD [18-19]. By interfering with effective communication, LD may be a socially disabling disorder with considerable psychosocial impact.

In addition to history and neurological examination, speech examination with nasolaryngoscopy is required for a definitive diagnosis [6]. Although dystonic spasms may occur during speech, the larynx should be structurally normal, with functional vocal cords. LD should be differentiated from muscle tension dysphonia (MTD) and essential vocal tremor (VT) although these can co-exist in up to one third of cases. Task-specificity is a core clinical feature of LD and helps to differentiate it from MTD and essential VT. The presence of a geste antagoniste, such as laughing or humming before speaking, further supports a diagnosis of LD.

LD is typically idiopathic, but symptoms may rarely occur secondary to structural brain disease or neuroleptic exposure. Up to 25.3% of patients with LD disclose a family history of dystonia, suggesting a genetic predisposition for a subset of cases. Indeed, LD has been associated with genes typically linked to generalised or segmental dystonia syndromes (DYT-TOR1A, DYT-TUBB4A, DYT-THAP1, DYT-GNAL and DYT-KMT2B) [18]. DYT-THAP1, in particular, may be associated with prominent LD20. DYT-TUBB4A, caused by missense mutation in the TUBB4A gene, is associated with 'whispering dysphonia'. The clinical phenotype of DYT-TUBB4A is heterogenous, ranging from isolated LD to severe generalised dystonia, accompanied by a 'hobby horse' ataxic gait [21].

Oromandibular dystonia

Oromandibular dystonia (OMD) is a focal dystonia involving the lower face, jaw and tongue. It is more common in women, with symptoms generally emerging in the fifth decade [22]. When accompanied by blepharospasm, it is termed Meige syndrome. OMD may be characterised by varying combinations of lip pursing, tongue dyskinesia, and jaw opening, closure, deviation, protrusion or retraction. The dystonia may occur spontaneously or may be task-specific, triggered by speech and mastication. As OMD impacts upon speech and eating, it may be a socially debilitating condition, with significant associated weight loss and impaired quality of life.

OMD may be idiopathic, a tardive phenomenon or a manifestation of an underlying hereditary condition, such as DYT-TOR1A dystonia, X-linked dystonia parkinsonism or neuroacanthocytosis [22]. Embouchure dystonia is a task-specific form of OMD affecting musicians who play brass and woodwind instruments. As illustrated by Table 1, numerous conditions may mimic OMD, including jaw tics, edentulous dyskinesia and jaw tremor, which may be essential or associated with parkinsonian conditions. Other mimics may include geniospasm, an autosomal dominant condition with early onset jaw tremor; hemimasticatory spasm, which may be associated with facial hemiatrophy; and bruxism, characterised by forced jaw closure and dental attrition during sleep or emotional distress. Diagnosis requires eliciting the positive features of dystonia, excluding negative features and identifying a geste antagoniste. Pertinent negative features include non-stereotyped or patterned movements, suppressibility, facial hemiatrophy, temporomandibular joint disorders, masticatory muscle weakness, edentulism or dental attrition, pain and other sensory symptoms, and autosomal dominant inheritance [3].

Limb dystonia

Numerous task-specific limb dystonias have been described, of which writer's cramp is the most common. These tend to occur in professionals engaging in repetitive highly skilled motor activities over prolonged periods of time. Writer's cramp affects adults between the ages of 30 to 50 years, presenting with an initial tension within the forearm, which culminates in cramp on writing with abnormal grip and posturing. On holding the pen, the thumb and index fingers develop abnormal postures, with excessive finger flexion, ulnar abduction and wrist flexion. There may be associated forearm supination and more proximal involvement of the arm and shoulder. Tremor accompanies less than one third of cases. The dystonia may remain task-specific or may affect other non-specific movements, resulting in complex writer's cramp [23].

Isolated adult-onset focal limb dystonia is typically sporadic but may be a manifestation of hereditary dystonic syndromes such as DYT-TOR1A, DYT-THAP1, or DYT-GCH1. Most focal limb dystonias affect the upper limb; leg onset should therefore raise the suspicion of a secondary cause [23]. As focal upper limb dystonias, such as writer's cramp, typically affect patients between the ages of 30 to 50 years, early onset before the age of 30 years is a clinical red flag. In such patients, genetic counselling and diagnostic testing for TOR1A is indicated [24]. Dystonic limb posturing may be associated with structural lesions of the basal ganglia, thalamus and brainstem, particularly when abrupt in onset or accompanied by additional neurological signs. Limb dystonia may also be the first manifestation of neurodegenerative disease, including Parkinson's disease, Wilson's disease, Huntington's disease, X-linked dystonia parkinsonism (DYT-TAF1) and neuroacanthocytosis. Although neuroleptic exposure typically produces craniofacial dystonia, limb involvement may occur [23]. As in Table 1, numerous conditions may mimic limb dystonia, including tics; functional movement disorders; stiff person syndrome spectrum disorders; orthopaedic or rheumatological disease, resulting in fixed abnormal postures; and neuromuscular weakness [3,23].

Conclusion

The focal dystonias are a rare and heterogenous group of conditions. In view of this, they are often not recognised by primary care physicians. Their phenomenological variability, combined with the potential for pseudodystonic conditions to mimic them, contributes to diagnostic delay and misdiagnosis. This paper provides an overview of the clinical classification and phenomenology of the focal dystonias as an aide to diagnosis. Early recognition of the stereotyped and patterned nature of dystonic movements is fundamental to accurate diagnosis. Expert recommendations can aid in the diagnosis of CD, OMD, LD and limb dystonia, and validated diagnostic guidelines exist for BSP. Video illustrations disseminated in journals and teaching material may assist in pattern recognition and diagnosis. A multidisciplinary approach can facilitate timely diagnosis and treatment, and has become an established part of the diagnostic process in some parts of the United Kingdom.

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Dominant parietal lobe ischaemic stroke presenting as alien hand syndrome

Abstract
We describe an unusual case of stroke manifesting as alien hand syndrome (AHS) causing sudden onset of abnormal hand movements. The patient reported his left arm would move outside his control and grab things in his surroundings without his conscious will. He felt his arm did not belong to him. Examination showed left arm brisk reflexes, astereognosis, and agraphesthesia in the left hand. Imaging revealed an established right parietal lobe ischaemic stroke. Lesions of the parietal cortex can cause AHS by disrupting the interpretation of somatosensory feedback when a movement is made and decreasing the ability to consciously monitor motor intentions. A low threshold should be adopted for arranging brain imaging and a thorough neurological examination is needed in any sudden onset movement disorder.

Alien hand syndrome (AHS) was first described in 1908 as a motor apraxia [1]. The term 'alien hand' originates from the French 'main étrangère' which Brion et al. used to describe the foreignness of the limb in patients with corpus callosum lesions [2]. AHS is defined by two criteria: the hand moves involuntarily and acts as though it has its own will [3]. Here, we report a case of AHS caused by a pure parietal stroke involving the postcentral gyrus.

Case presentation

A 70-year-old right-handed man presented to the movement disorders clinic reporting that his left arm was 'jumping all over the place'. His symptoms started a month earlier, when his arm movements suddenly woke him up from sleep, touching him and moving spontaneously outside his control. His arm would shoot upwards, needing to be controlled by his right hand. It would grab things in his surroundings without his conscious will, and he felt it did not belong to him. This caused difficulties with tasks requiring both hands, such as buttoning his shirt. His left arm was not weak, but he was unable to maintain its posture and struggled to hold a cup. The other limbs, face, vision, and speech were not affected. His past medical history included hypertension and hyperlipidaemia, and medications included aspirin, atorvastatin, lansoprazole, and naproxen.

On examination, his cranial nerves were intact apart from a mild left facial droop. Power and sensation to pinprick, fine touch, and vibration sensation were normal in all four limbs. However, he had astereognosis and agraphesthesia in the left hand, suggesting cortical sensory loss. He had mild left dysdiadochokinesia and bilateral intention tremor, but no bradykinetic rigidity. Reflexes were brisk in the left arm and plantar responses were flexor bilaterally. There was no ataxia.

His MRI brain showed an established ischaemic stroke in the right postcentral gyrus of the parietal lobe, best seen on the fluid attenuation inversion recovery images (Figure 1), which was the correct age for when his symptoms started.

At follow-up after six weeks, the patient reported that the involuntary movements of his left arm reduced dramatically to become very infrequent, which do not affect him significantly. He no longer reports the feeling of foreignness.

Discussion

In a literature review by Scepkowski et al, frontal, callosal, and posterior subtypes were used to describe AHS [4]. The frontal type afflicts the dominant hand, resulting from left medial frontal and callosal damage. Patients develop a grasp reflex and compulsive tool manipulation. Damage to the corpus callosum with or without bilateral or right frontal lesions causes the callosal type, affecting the non-dominant hand. In this type, patients develop inter manual conflict, where one hand acts at cross-purposes with the other. Posterior AHS is less commonly described and is caused by injury to the thalamus and parietal, occipital, and temporal lobes. It causes uncoordinated purposeless hand movements, arm levitation, and a feeling of foreignness.

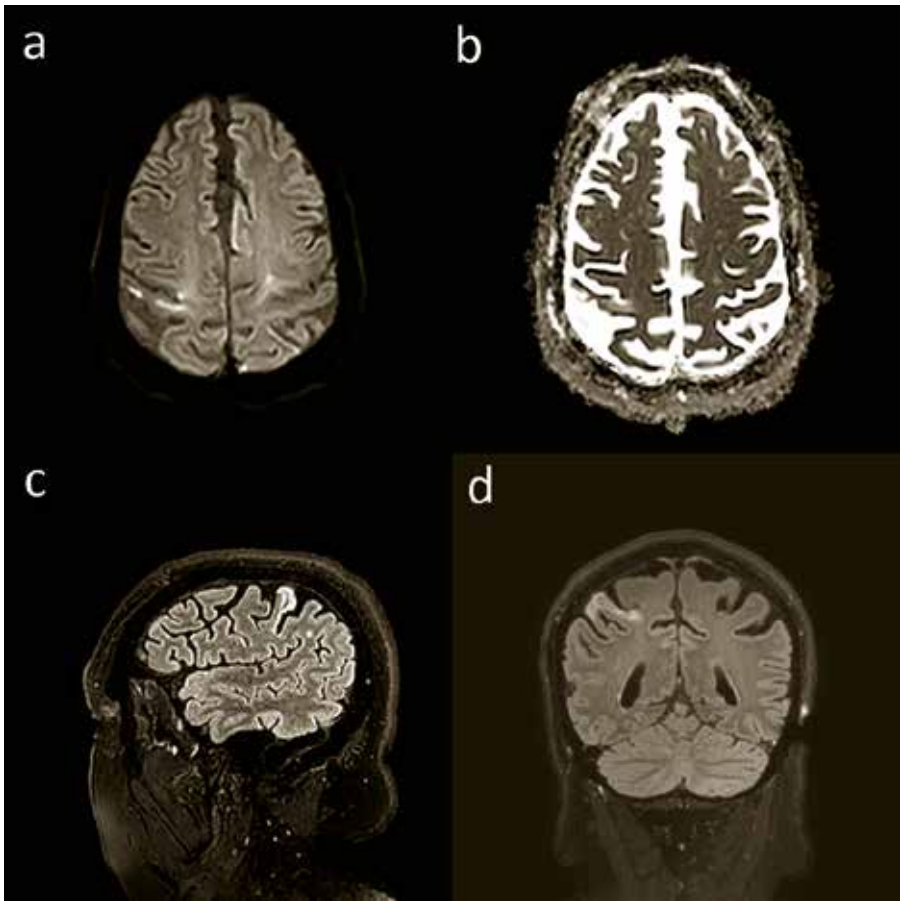

Figure 1: Brain MRI showing established right postcentral gyrus cortical infarction, with gliosis and volume loss of the right paracentral gyrus in keeping with an area of established cortical infarction. a) Diffusion weighted image. b) Apparent diffusion coefficient map. c) and d) Fluid attenuation inversion recovery images.

Several neurological conditions can cause AHS other than stroke, including brain tumours, corpus callosum surgery, aneurysms, or degenerative disease. Corticobasal degeneration (CBD) is a rare neurodegenerative disease involving the cerebral cortex and the basal ganglia. It can cause AHS, but additionally causes parkinsonism, apraxia, aphasia, and dementia [5]. This diagnosis was ruled out as it is also characterised by an insidious onset and progressive course. Our patient's symptoms were of sudden onset and got progressively better. Also, examination did not reveal any parkinsonism and the patient had normal cognition. In addition, the MRI did not display the classical pattern of atrophy seen with CBD, although certain cases of CBD may show global atrophy alone and not a specific pattern [6].

The patient does not have a history of neurosurgery and the brain MRI scans did not show any evidence of masses or aneurysms, which ruled out vascular malformations as a cause.

Another differential diagnosis was cerebral amyloid angiopathy (CAA) which is a common age-related cerebral small vessel disease characterized by the progressive deposition of β-amyloid in the wall of cortical and leptomeningeal small arteries [7]. It can cause transient focal neurological episodes including limb jerking [8]. This can resemble the involuntary arm movements of AHS. CAA is also a common cause of lobar intracerebral haemorrhage (ICH) [9]. CAA was important to be excluded as antiplatelet therapy is a risk factor for ICH. Although the MRI changes for CAA and ischaemic stroke can be similar, no evidence was found of bleed or microhaemorrhage on blood-sensitive MRI, excluding CAA as a cause. The permanency of the symptoms also goes against a CAA diagnosis.

A literature review by the authors revealed 12 cases of AHS caused by isolated parietal lobe lesions. However, none of the cases exhibited all four features of involuntary hand movements, arm levitation, feeling of foreignness, and cortical sensory loss present in our case. We also demonstrate that an infarct limited to the postcentral gyrus can cause AHS.

Previous work using functional MRI has shown that AHS caused by parietal stroke was associated with isolated activation of the contralateral primary motor cortex, as opposed to the orchestrated activation of neural networks when a voluntary movement is made [10]. The premotor cortex generates an internal copy of a movement which is relayed to the somatosensory cortex of the parietal lobe. The somatosensory feedback generated by a movement is compared to this internal copy. If they correlate, the movement is interpreted as self-generated rather than due to an external force. In AHS, there is a deficit in creating this internal model, causing the individual to mistakenly interpret a self-generated movement as one produced by an external force [11].

Our patient was able to grasp an object in his left hand; however, he would drop it soon after, indicating a failure to maintain the action possibly due to the inability to consciously monitor his motor intention. Sirigu et al. showed that the parietal lobe plays a critical role in this function and suggests that parietal lobe stroke can cause AHS by disrupting cortico-cortical sensorimotor processing loops responsible for the awareness of the motor movement [12].

Key points

1. AHS is a rare stroke chameleon and can be caused by cortical parietal stroke.
2. A thorough neurological examination may reveal additional deficits such as sensory changes, visual field defects, and brisk reflexes related to stroke.
3. A low threshold should be adopted for arranging brain imaging when patients present with movement disorders in the acute setting.

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The fatal illness of Oscar Wilde

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Figure 1

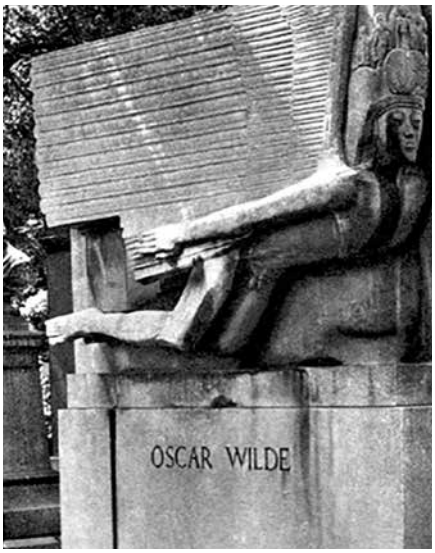

Figure 2

Abstract
The literary genius of Oscar Wilde has been sullied and besmirched by his infamous entanglement with Lord Alfred Douglas for "gross indecency" leading to his subsequent imprisonment for two years. After release he developed what was certified as "cerebral meningitis" in November 1900, from which he died. The much disputed cause is discussed. The claims for neurosyphilis are wholly inadequate; a chronic middle ear infection with cholesteatoma and intracranial suppuration is here suggested as the basis of his fatal illness. Had he lived in the 21st century Oscar Wilde would not have been so cruelly punished, may have received effective treatment, and thus been spared to provide much more of his wit and elegant plays, stories and poetry.

> *Experience is the name everyone gives to their mistakes.* Oscar Wilde

The literary output of the comic genius Oscar Fingal O'Flahertie Wills Wilde (1854-1900) (Figure 1), his elegant, entertaining plays, magical children's stories, and wonderful witticisms need no reprise [1]. Wilde's well-publicised affair with Lord Alfred Douglas caused his father, the Marquess of Queensberry to leave his calling card at Wilde's club, the Albemarle, on 18 February 1895. On it was inscribed: "For Oscar Wilde, posing somdomite*". Oscar Wilde foolishly initiated a private prosecution against Queensberry for libel, held on 3rd April 1895. Three days later he was arrested for "gross indecency" and after two further trials was sentenced to two years' penal servitude with hard labour in Newgate then Wandsworth prisons, and finally to Reading gaol. Whilst in Reading his letter to Lord Alfred Douglas, *De Profundis* (published 1905), records a man fallen from the throne of social and literary glory to the dungeon of public degradation. Wilde confessed his own "pit of shame" and vainglorious behaviour; he sought redemption.

> *Terrible as was what the world did to me, what I did to myself was far more terrible still.… There is only one thing for me now, absolute humility.*

He was released on 19 May 1897 and sailed that evening for Dieppe, where he lived in self-imposed exile, never to return to England [2]. To avoid public attention he adopted the name Sebastian Melmoth, and his wife, Constance (née Lloyd) changed her surname, and those of their sons to Holland.

Following his release and self-ordained exile his literary skill waned and he wrote only the maudlin ballad, *The Ballad of Reading Gaol*: a recognition of a universal human paradox.

…In Reading gaol by Reading town
There is a pit of shame,
And in it lies a wretched man
Eaten by teeth of flame,
In a burning winding-sheet he lies,
And his grave has got no name. …

And all men kill the thing they love,
By all let this be heard,
Some do it with a bitter look,
Some with a flattering word,
The coward does it with a kiss,
The brave man with a sword.

The first indication of his fatal illness is when in Reading gaol he fainted in the chapel and injured his ear, though which side is unknown. He became deaf and the ear would bleed intermittently. He later developed persistent headaches. He consulted British embassy GP, Dr Maurice a'Court Tucker whom his devoted former lover Robbie Ross considered a silly, kind, excellent man [3]. Tucker called in an otologist Dr Claisse**, who on 10th October I900, performed an unspecified ear operation, probably a mastoidectomy for cholesteatoma. His health temporarily improved but he reverted to his old habits of gross overeating and excessive consumption of brandy, wine and absinthe. Not surprisingly his health declined. He became stout, and was likened to the gluttonous Roman Emperor Vitellius. A Dr Hennion warned Ross that Oscar could not live more than three or four months unless he altered his way of life. He also had a fluctuating red skin lesion which he mistakenly attributed to mussel poisoning. It is consistent with, but unlikely evidence of secondary syphilis.

By 25 November 1900 he developed "cerebral meningitis". His friend Robbie Ross arrived on 29 November, sent for a priest, and Wilde "in a semi comatose state" was conditionally baptised and given the Last Sacraments into the Catholic Church by Fr Cuthbert Dunne of Dublin. Wilde died the next day.

Cause of death
The certified cause of death was cerebral meningitis. Many of the early descriptions of his malady are shrouded by Wilde's self dramatisation and biographical argument with inadequate records of his physicians and surgeons. The problem of this last illness has constituted an interesting case for commentary [3].

A frequent suggestion was neurosyphilis. As an Oxford undergraduate he may according to Ellman have contracted syphilis from a female prostitute [5,6]. Dr Tucker thought syphilis the cause of his illness but Wilde was examined by at least seven doctors, including two psych-

iatrists in Reading gaol and none had diagnosed syphilis nor disclosed evidence of tertiary lesions [7]. The evidence that Wilde had ever contracted syphilis is sketchy and based more on gossip than on objective clinical facts [4]. Supported by Robins and Sellars [8], Terence Cawthorne, a distinguished otologist gave convincing evidence that the probable cause of Wilde's final illness was intracranial suppuration (pyogenic, not syphilitic) resulting from otitis media [9].

Oscar's father Sir William Wilde was eccentric and promiscuous, but an excellent oculist and Ear Nose and Throat surgeon. It is not without irony that he observed in his *Practical Observations on Aural Surgery and the Nature and Treatment of Diseases of the Ear* (1853):

> *So long as otorrhoea is present, we never can tell, how, when or where it will end, or to what it may lead.*

A curious coincidence is that his son, Vyvyan Holland, an author and translator, required ear surgery for mastoid infection only eight weeks after his father's death.

Oscar Wilde's body was deposited in a pauper's grave in Bagneux cemetery, Paris. Nine years later Robbie Ross aided by donations from Wilde's admirers transferred his remains to Père-Lachaise cemetery in July 1909. There, a sculpture by Jacob Epstein (Figure 2) bears the epitaph from *The Ballad of Reading Gaol*:

And alien tears will fill for him
Pity's long-broken urn,
For his mourners will be outcast men,
And outcasts always mourn.

Had he lived in the 21st century the genius that was Oscar Wilde would not have been so cruelly punished. If only modern experience: "the name everyone gives to their mistakes" could have prevailed in his lifetime, his further writing would have enhanced our literature and shamed our past.

*Queensberry's misspelling of "sodomite"

**Sometimes referred to as Dr Klein or Dr Kleiss [4]

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Professor Pam Enderby: "The Rockstar of Speech and Language Therapy!" By Neil Bindemann

One afternoon in 2021 my wife was talking with a lady wishing to book an appointment with the consultant physician she worked with. The lady mentioned that she was a Speech and Language Therapist, and as part of her calming approach to patients and knowing of Pam, due to my work, my wife asked if she knew Pam. The lady replied, "Oh yes, she is regarded as the rockstar of speech and language therapy". Having worked with Pam since 2006, which has been both a joy and privilege, this is one of best descriptions that I have heard.

Professor Pam Enderby

In November, allied health professionals and therapists from across the UK will come together at TOMs CONNECT 22 to celebrate over 40 years of measuring therapy outcomes.

Earlier this year, as part of the run up to the event, I tweeted a clip from an informal conversation I had with Pam from the 2020 conference. The clip, which has been viewed more than 3000 times, shares 2 magical moments: how her career began and her passion for speech and language therapy, which was influenced by her father having 3 strokes.

The tweeted replies give a sense of how people who have worked with Pam feel about her and the work that she has done throughout her career.

- "What a legend Prof Enderby is in our field! I'm glad she persisted with #salt #SLT"
- "A legend in her lifetime of rehabilitation research...A #SpeechAndLanguageTherapy history maker."
- "Is it no wonder that Pam Enderby is a national, nay international treasure? I have admired her so much over the years and find it incredible that her energy and passion for SLT has never waned. Loving her stewardship of IALP too. Enjoyed this recorded interview very much"
- "An inspiring lady who continues to support the world of rehabilitation research through the likes #outcomedata research"
- "An amazing career and truly inspiring woman"
- "A must see – such an inspiration and what impact Pam has had on so many lives on so many ways"

Professor Diane Playford has worked and collaborated with Pam, and offers these thoughts:

"Pam has been a driving force in speech therapy and rehabilitation for as long as I can remember. She is a powerful advocate for speech therapy, multidisciplinary working, rehabilitation of all kinds but most of all the patients. Personally, I've always enjoyed her company, she is energetic, knowledgeable, thoughtful, and funny. She isn't afraid to challenge ideas, and where necessary individuals, but she is generous with her time and expertise and kind when providing feedback. Her contribution to speech and language, looking at structure and processes needed to deliver rehabilitation, and measuring outcome is unparalleled. On any measure of excellence, Pam would score above the ceiling!"

So, we invite you to TOMs CONNECT 2022, a day of celebration in November at Edgbaston Cricket Ground, Birmingham. The event will showcase how more than 40 years of measuring therapy outcomes have contributed to providing so many services across the UK, and now internationally, with data and evidence to highlight their impact and value.

To learn more about the conference, which all ACNR readers can attend with a special discount, please visit www.communitytherapy.org.uk. To request the code, please email info@communitytherapy.org.uk and add ACNR discount enquiry in the subject of the email.

To watch the interview with Pam, when she talks with Neil Bindemann about her father's strokes being an influence in her speech and language career, go to https://vimeo.com/474646063

Cure Parkinson's Spring Research Update meeting

Conference details: 4 May, 2022, International Student's House, London, UK and streamed virtually. ***Report by:*** Angelika Zarkali, Neurology Registrar, St George's Hospital and post-doctoral Clinical Research Fellow in the Dementia Research Centre, University College, London, UK. ***Conflict of interest statement:*** Angelika Zarkali is ACNR's Conference News Editor.

This was a hybrid meeting with participants meeting in-person as well as participating via a live-stream. The hybrid format had some initial hiccups with sound issues, but it worked well overall and allowed participants from across the country – including myself – to attend this interesting event!

The meeting started with a welcome from Dr Richard Wyse who gave background information about the topic and an overview of the timeline of how the link between Parkinson's disease (PD) and diabetes was unravelled.

Dr Alastair Noyce from Queen Mary University of London, UK then presented evidence for the association between type 2 diabetes (T2DM) and Parkinson's risk/severity. Dr Noyce presented us with intriguing data from a number of laboratories including his own, which showed a clear epidemiological link between Parkinson's Disease and T2DM with the risk of Parkinson's Disease increasing the longer an individual has type 2 diabetes. In addition, patients with Parkinson's Disease who also have diabetes have a worse phenotype with worse motor and cognitive symptoms and more aggressive progression. He then described an ongoing study assessing blood biomarkers in patients with Parkinson's Disease with and without T2DM, again showing higher levels of blood biomarkers of axonal damage such as neurofilament levels in patients with diabetes compared to patients with Parkinson's Disease without diabetes; this effect was even more pronounced in patients with uncontrolled diabetes. Dr Noyce discussed causality and the need for further research but planted the seed to the audience that we could potentially prevent or treat Parkinson's Disease by treating T2DM.

Professor Michele Tagliati from Cedars Sinai, US talked about the potential use of liraglutide, an antidiabetic medication in the treatment of Parkinson's. He discussed the results of a randomised controlled study assessing cognitive, motor and non-motor symptoms in patients with Parkinson's Disease treated with liraglutide versus a placebo. After 1 year there was no significant difference in cognitive or motor performance but there was a significant improvement in non-motor scores (across all symptom domains) in patients treated with liraglutide. Secondary outcomes including the global Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores, activities of daily living and quality of life measures also showed improvement in patients after one year of being treated with liraglutide. Overall, although still early days, his talk highlighted liraglutide as a potential emerging therapeutic in Parkinson's Disease.

After a short break, Dr Dilan Athauda from University College London, UK, discussed the use of another diabetic medication, exenatide, for the treatment of Parkinson's Disease. He provided compelling evidence that exenatide does have potential as a treatment for Parkinson's disease. Perhaps even more exciting was his suggestion that early recent evidence from animal models of Parkinson's suggest that dual GLP1 agonists may be even more effective than exenatide in preventing neuronal loss. He finished by discussing his plans for research using human induced pluripotent stem cells to model Parkinson's disease and to trial these dual agonists in the lab to evaluate different agonists to decide which should be taken to clinical trials.

The day finished with an overview of the multitude of clinical trials examining GLP-1 agonists in the treatment of Parkinson's Disease by Dr Selen Yalkic; with more than 8 studies currently underway around the world with results in the coming months and years, it will surely be an interesting and evolving research area! This is why a specific GLP-1 meeting is planned in Madrid to bring together the key investigators working in the field and to plan for a regulatory process and potential off-label use.

After a Q&A session, the day came to an end on a rather hopeful note, knowing the potential that antidiabetic medications could play in the future in Parkinson's disease. Individuals living with Parkinson's disease and all health professionals involved in their care will surely be waiting impatiently to see the results of the various clinical trials!

You can watch the presentations, and the recordings of the key speakers at https://cureparkinsons.org.uk/2022/03/spring-research-update-2022/

The European Stroke Organisation Conference 2022

Conference details: 4-6 May 2022, Lyon, France. Conference also streamed virtually. ***Report by:*** Martin Punter, Consultant Neurologist, Wellington Regional Hospital and Clinical Senior Lecturer at the University of Otago, Wellington, New Zealand. ***Conflict of interest statement:*** Martin Punter is ACNR's Stroke Editor and an ESO member.

After more than a year of virtual meetings and conferences, neurology colleagues from Europe and around the world were finally able to meet up at the European Stroke Organisation Conference, a hybrid meeting online and in the magnificent city of Lyon between the 4th and 6th May 2022.

The conference began with a welcome from Joanna Wardlaw followed by presentation of the results from recently completed large clinical trials. Highlights from this session included Bijoy Menon and Richard Swartz's presentation of the results of the ACT trial demonstrating non-inferiority of tenecteplase to alteplase and the results of the TASTE-A trial, a first pre-hospital thrombolytic trial. This trial demonstrated the benefit of tenecteplase over alteplase on CT-perfusion lesion size following treatment as well as greater ultra-early clinical improvement. At the end of the session Raul Nogueria presented the results of the ATTENTION trial, finally demonstrating that the overwhelming efficacy of endovascular therapy persists in the posterior circulation leading to improvements in disability and mortality.

The welcome session was followed by a lunch break and then parallel sessions including service organisation, rehabilitation, neurointerventional therapy, cognition and vascular cognitive impairment, risk factors and primary prevention, aetiology and pathophysiology and teaching sessions on thalamic stroke and cerebral hypoperfusion. A session dedicated to levelling up stroke care in Europe including in rural versus urban centres, stroke care for migrants and homeless populations, and care of populations and staff in conflict zones was also included.

Day two started with seven parallel scientific sessions and two teaching sessions covering diverse topics ranging from epidemiology and imaging to covert stroke and the front-line of neurointervention: direct to mothership angiosuite or mothership to patient. Immediately following the coffee break

Martin Dichgans (Germany) and Else Sandset (Norway) chaired the second large clinical trials session. Before the presentations of the trials the two ESO award winners were presented, Valeria Caso, Past President of ESO was presented with the President's Award and Guillaume Turc was presented with the ESO Scientific Excellence Award. On completion of the presentation of the Angels Awards to hospitals from ESO countries leading on quality measures the presenters of the large clinical trials took the floor. Christopher Schwarzbach presented the results of the Interstroke Study showing that acute febrile illness is associated with increased odds of ischaemic stroke in most parts of the world and vaccination for influenza associated with decreased odds. The following two talks highlighted atmospheric pollutants and epigenomic age both as risk factors for stroke (Kongbunkiat and Szejko, respectively). Dr Kamtchum then presented their study linking circulating IL-6 levels with higher risk of progression of atherosclerosis and postulating a potential avenue for therapy in those patients not eligible for carotid revascularisation. Rounding off the session, Dr Verhoeven reported the results from the Netherlands of a greater than two-fold increased risk and five times increased risk of cancer diagnosis for younger patients within the first year after ischaemic or haemorrhagic stroke respectively. More work will be needed in order to identify characteristics that might support targeted screening.

The scientific presentations continued after lunch with parallel joint symposia with the European Society of Cardiology exploring the evaluation of cardiac source of stroke and the European Society of Neurosonology and Haemodynamics updating the key aspects in neurosonology. In addition to other symposia including discussions on the role of artificial intelligence and data science in improving stroke care, stroke care in women from pathophysiology to healthcare delivery, reducing waste in stroke research, and the opportunity for teaching on imaging in acute stroke, treatment challenges, management of seizures, and secondary prevention after stroke were available.

On the final day of the conference, the morning was jam-packed with more parallel sessions of stroke science kicking off with a joint symposium with the Pre-hospital Stroke Treatment Organisation putting the spotlight on mobile stroke units and other technologies to enhance the pre-hospital assessment and care of patients with stroke. The morning included discussions on genetics, individualised stroke care and personalised medicine as well as further teaching courses on ischaemic and haemorrhagic stroke. During these parallel sessions the latest ESO guidelines were presented on unruptured aneurysm, secondary prevention, intracranial atherosclerosis, and screening atrial fibrillation in cryptogenic stroke. Before the closing ceremony the onsite television station, ESOC TV reviewed the highlights of the conference beginning with an overview of the work of SAFE in reducing the burden of stroke in Europe

Raul Nogueria presented the results of the ATTENTION trial


Valeria Caso, Past President of ESO was presented with the President's Award

by collaboration across the continent, including the not insignificant surprise and challenges of COVID. Colleagues also found the highlights of the meeting being the chance to meet with colleagues, some of whom had only ever been encountered on Zoom, the chance for students and trainees to present in person for the very first time, and the technical success of the online platform as an adjunct to such a successful meeting allowing participation from scientists and clinicians who would otherwise have been unable to attend. We were then encouraged to stay in tune for the final large clinical trials session and look forward to ESOC Munich 2023.

The final large clinical trials session presented a wide range of studies starting with some promising data on adjunctive treatment with Glenzocimab to reduce symptomatic and asymptomatic haemorrhage after reperfusion therapy, though larger trials are needed to confirm efficacy. We next heard from the phase II TEXAIS trial, aiming for better post-stroke glycaemic care but unfortunately a casualty of COVID, stopping early for time constraints. Despite this there is support for the safety of Exenatide after acute ischaemic stroke and a larger clinical trial is planned. Craig Anderson presented insights from further analysis of the ENCHANTED trial which had previously demonstrated reduced chance of symptomatic ICH by intensive blood pressure monitoring after intravenous thrombolysis. The data showed no evidence of increase in infarct volume by early intensive blood pressure lowering in thrombolysed patients. Anna Ramos presented the secondary results of the RACECAT trial. This study of drip-and-ship vs mothership model of treatment showed no evidence of benefit for patients with intracerebral haemorrhage at the expense of a higher rate of transfer complications. Joji Kuramatsu reported the results of an individual patient level data meta-analysis on thrombolytic therapy for intraventricular haemorrhage. Improvements in disability at six months were observed especially in those patients treated within 48 hours. One particularly interesting highlight in this session was the presentation from an international multi-centre cohort study analysing the safety of intravenous thrombolysis in patients taking direct oral anticoagulants. Despite over 40% of included patients being treated with intravenous thrombolysis despite DOAC levels/status not being tested or known, this study offers reassuring safety data. Tenecteplase was reported on again in the TWIST trial assessing the drug vs placebo in patients treated within 4.5 hours after wake-up stroke and no significant difference was found between groups on primary outcome mRS shift analysis at 90 days. The final scientific presentation of the session, day, and conference was the results of the BAOCHE trial, an EVT study from China of patients presenting within 6-24 hours from last seen well and with small to moderate infarct burden on non-contrast CT scan. Although no benefit in mortality was observed, the trial was stopped early due to safety as interim analysis showed a significant benefit of EVT in achieving mRS 0-3 over best medical therapy, further cementing the role of EVT for basilar artery occlusion.

Peter Kelly, the current ESO president closed the meeting with a video review of this ESOC 2022 meeting in Lyon, France. Throughout the conference the presentation of highlights and discussions with experts in the field has been easily available online. ESOC TV was, for me, one of the highlights of the congress as a virtual attender but I, for one, am excited about being able to attend in person for ESOC 2023 in Munich.

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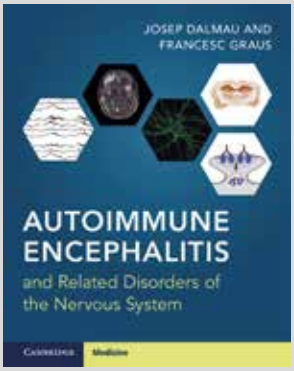

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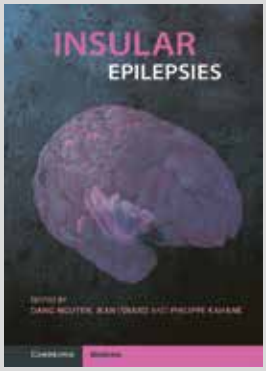

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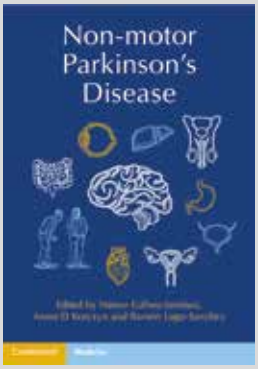

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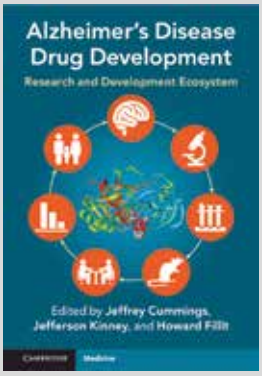

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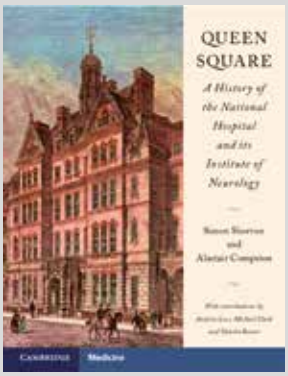

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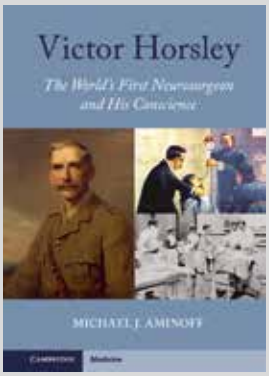

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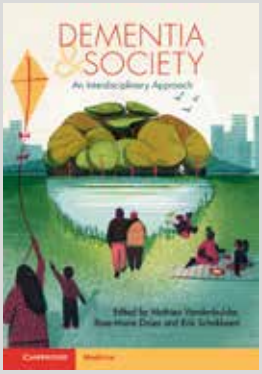

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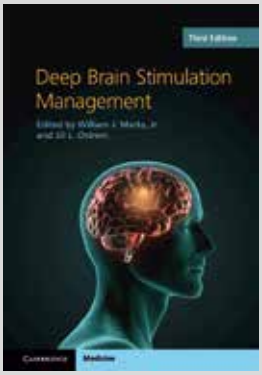

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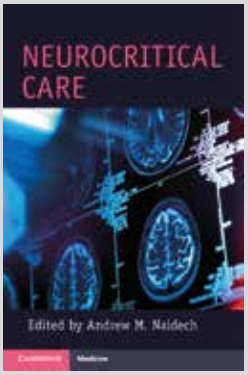

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