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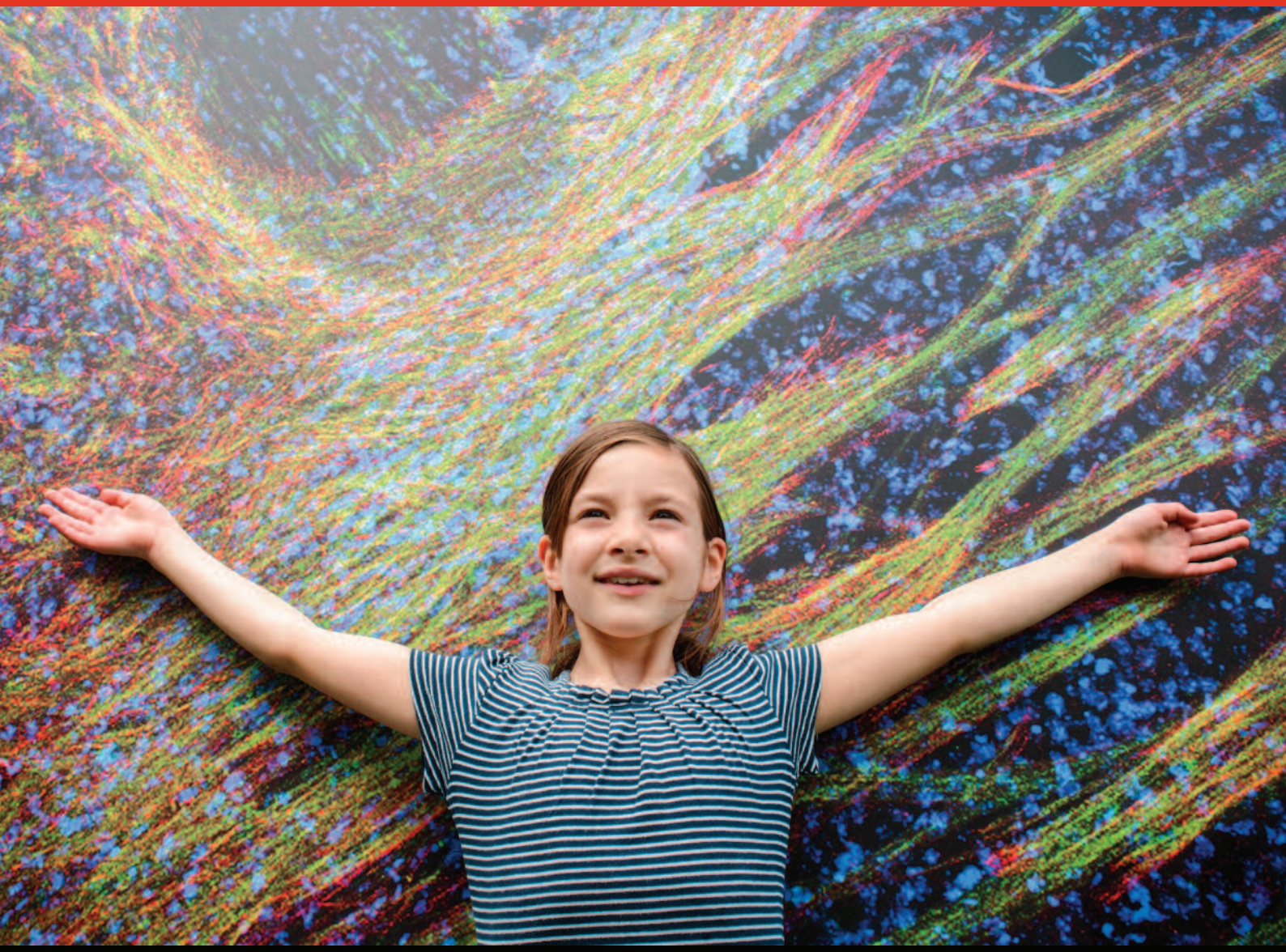
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

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Once-daily

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Abbreviated Prescribing Information. AUBAGIO▼ 14 mg film-coated tablets. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. **PRODUCT COMPOSITION:** Each film-coated tablet contains 14 mg of teriflunomide. **INDICATIONS:** AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). **DOSAGE AND ADMINISTRATION:** The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. The recommended dose of teriflunomide is 14 mg once daily. The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. AUBAGIO can be taken with or without food. ***Elderly population***: AUBAGIO should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy. ***Renal impairment***: No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis. ***Hepatic impairment:*** No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. ***Paediatric population***: The safety and efficacy of AUBAGIO in children aged from 10 to less than 18 years has not yet been established. **CONTRAINDICATIONS:** Hypersensitivity to the active ingredient or excipients. Severe hepatic impairment (Child-Pugh class C). Pregnant women, or women of childbearing potential not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/l. Breast-feeding women. Severe immunodeficiency states, e.g. AIDS. Significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia. Severe active infection until resolution. Severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group. Severe hypoproteinaemia, e.g. in nephrotic syndrome. **EDUCATIONAL GUIDANCE**: Prior to prescribing AUBAGIO, physicians must familiarise themselves with educational materials which consist of a *Healthcare Professional Education/Discussion guide* and they should provide their patients with a *Patient Card* and *Patient Leaflet*. **WARNINGS AND PRECAUTIONS:** ***Monitoring***: *Before starting treatment* the following should be assessed: blood pressure, alanine aminotransferase (ALT/SGPT), complete blood cell count (CBC) including differential white blood cell (WBC) and platelet count. Exclude pregnancy. *During treatment* the following should be monitored: blood pressure, ALT/SGPT. A CBC should be performed based on signs and symptoms. ***Accelerated elimination procedure:*** Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide. (For further information, please refer to the SmPC). ***Hepatic effects:*** Assess liver enzymes before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. Teriflunomide therapy should be discontinued if liver injury is suspected and discontinuation should be considered if liver enzymes are confirmed as >3x ULN. Patients with pre-existing liver disease may be at increased risk of developing elevated liver enzymes when taking teriflunomide and should be closely monitored for signals of liver disease. AUBAGIO should be used with caution in patients who consume substantial quantities of alcohol. ***Blood pressure***: Must be checked before the start of teriflunomide treatment and periodically thereafter. ***Infections:*** Patients receiving AUBAGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with AUBAGIO until the infection(s) is resolved. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with teriflunomide. ***Haematological effects***: A mean decrease of less than 15% from baseline affecting white blood cell counts have been observed. Obtain complete blood count with differential prior to initiation of treatment, thereafter CBC should be assessed as indicated by clinical signs and symptoms. In patients with pre-existing cytopenias there might be a higher risk of haematological disorders with teriflunomide. In cases of severe haematological reactions, including pancytopenia, AUBAGIO and all concomitant myelosuppressive treatment must be discontinued and the accelerated elimination procedure be considered. ***Respiratory reactions***: Due to the potential risk of interstitial lung disease, pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. ***Skin reactions:*** In case of ulcerative stomatitis, or if skin and /or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions, teriflunomide must be discontinued and an accelerated procedure initiated immediately. ***Immunosuppressive/Immunomodulating therapies:*** Co-administration with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. ***Peripheral neuropathy***: Confirmed peripheral neuropathy, consider discontinuing AUBAGIO therapy and performing the accelerated elimination procedure. ***Vaccination***: Live attenuated vaccines should be avoided. **SWITCHING to or from AUBAGIO:** No waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate. Due to the risk of concomitant immune effects for up to 2-3 months, caution is required when switching patients immediately from natalizumab to teriflunomide. To avoid concomitant immune effects when switching from fingolimod, 10-14 weeks is needed for lymphocytes to return to the normal range. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months, although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated. **CONCOMITANT USE AND DRUG INTERACTION:** Co-administration of teriflunomide with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. Rifampicin and other known potent CYP and transporter inducers, medicinal products metabolised by CYP2C8, oral contraceptives, medicinal products metabolised by CYP1A2, OAT3 substrates, BCRP substrates and OATP substrates should be used with caution during treatment with teriflunomide. For patients receiving teriflunomide treatment with cholestyramine or activated charcoal is not recommended. For co-administration of warfarin with teriflunomide, close INR follow-up and monitoring is recommended. **PREGNANCY AND LACTATION:** ***Pregnancy:*** Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. In case of suspicion of pregnancy, patient must notify the physician. In case of pregnancy, the physician and patient must discuss the risk to the pregnancy and the accelerated elimination procedure. In women wishing to become pregnant, teriflunomide should be stopped and an accelerated elimination procedure is recommended (Please refer to the SmPC for further information). Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens during the accelerated elimination procedure. Use of alternative contraceptive methods is recommended. ***Lactation***: Breast-feeding women must not receive teriflunomide. **UNDESIRABLE EFFECTS:** Based on placebo-controlled studies the most commonly reported adverse reactions in the teriflunomide treated patients were: influenza, upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, increased ALT, nausea, and alopecia. ***Very common (≥ 1/10)*** Influenza, upper respiratory tract infection, urinary tract infection, paresthesia, diarrhoea, nausea, alopecia, ALT increase. ***Common (≥ 1/100 to < 1/10):*** Bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, neutropenia, mild allergic reactions, anxiety, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia, peripheral neuropathy, hypertension, vomiting, toothache, rash, acne, musculoskeletal pain, myalgia, pollakiuria, menorrhagia, pain, GGT increase, AST increase, weight decrease, neutrophil count decrease, WBC decrease, post-traumatic pain. For listings and further information on adverse reactions, please refer to the SmPC. **Legal Classification:** POM (Prescription Only Medicine). **List Price:** £1037.84 per 28 day pack. **MARKETING AUTHORISATION NUMBER:** EU/1/13/838/001-005. **MARKETING AUTHORISATION HOLDER:** Sanofi-Aventis Groupe. 54, Rue La Boétie. F-75008 Paris. France. **FULL PRESCRIBING INFORMATION AVAILABLE FROM** Genzyme Therapeutics Ltd, 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford OX4 2SU. **DATE OF PREPARATION:** October 2013.

▼AUBAGIO is subject to additional monitoring. This will allow quick identification of new safety information. Adverse Events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard Adverse events should also be reported to Genzyme Tel: 01865 405 200

References: 1. AUBAGIO (teriflunomide) Summary of Product Characteristics. November 2013. **2.** Confavreux C, O'Connor P, Comi G *et al.* Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* January 2014 [Published online]. DOI: 10.1016/ S1474-4422(13)70308-9. **3.** O'Connor P, Wolinsky JS, Confavreux C, *et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* 2011; 365(14): 1293-1303. **4.** Confavreux C, Li DK, Freedman MS, *et al.* Teriflunomide Multiple Sclerosis Trial Group. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. *Mult Scler.* 2012 Sep; 18(9): 1278-89.

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Conference Report
ABN conference report

Pictures in the park

Natasha Kind in front of 'Sensory Superhighway'. Courtesy of Callum Bennetts at Maverick Photoagency Ltd. Natasha is the daughter of Peter Kind, Co Curator and Professor of Developmental Neuroscience and Director of The Patrick Wild Centre.

ACNR's cover picture this issue shows one of the striking images capturing the beauty and complexity of the brain that have been on display in St Andrew Square, Edinburgh.

The pictures showcased research by the University of Edinburgh that seeks to improve our understanding of the brain and how it is altered in people with learning disabilities and other neurological conditions.

'The brain – is wider than the sky' included snapshots that pinpoint the effects of neurological disorders such as autism and Fragile X Syndrome, the most common cause of inherited intellectual disability.

The 38 images highlighted the advanced technologies used by the University to visualise brains and their cells in action.

Researchers from the University's Patrick Wild Centre for Research into Autism, Fragile X Syndrome and Intellectual Disabilities collaborated with the Scottish charity Mindroom, to devise the exhibition.

Sophie Dow, founder of Mindroom, said: "These images are simply too beautiful to be hidden away in a lab. They were created to further our understanding of the brain but they can also be viewed as stunning examples of abstract art. Our hope is that people admiring the pictures on show will also come away with a greater awareness of what it means to be affected by learning difficulties and other brain conditions."

Professor Peter Kind, Director of the Patrick Wild Centre, said: "Each of these images tells a story about vital brain research that is taking place right here in Edinburgh. We are delighted to offer people a rare glimpse into our work in such a prestigious location at the heart of our city."

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Mike Zandi, Editor.

This issue has a therapeutics theme. Our two review articles tackle disease-modifying therapy trials in Parkinson's disease. In one, we are pleased to introduce a new series of articles on regenerative neurology. Roger Barker, from Cambridge, who co-ordinates the TRANSEURO consortium[1] and edits this series, introduces the first article on page 26.

We start with an introduction of cell therapies in Parkinson's Disease, and on what has been learnt from earlier clinical trials, by Malin Parmar and colleagues from Lund. The path from a basic neuroscience discovery to completion of phase 3 clinical trials in people can be long, painful and expensive. Jonathan Evans, from Norwich, reflects on innovative trial designs which may help us to bring novel therapies for Parkinson's Disease to the clinic in a faster and far more effective way than before. Jonathan expounds the pros and cons of drug repurposing, adaptive trials and seamless transitions, tells us about the 'lessebo effect,' how to retain the ability to detect a clinically meaningful effect and more in his article. We are grateful to have Sheila Roy write her own personal account of the Prosavin gene therapy on page 15 to remind us all why we should keep going.

Trial methodology comes up again in the article by Josef Alawneh, Cambridge and Jean-Claude Baron, Paris, who discuss the imaging of the ischaemic penumbra in stroke. This is an excellent and authoritative article detailing a body of work, introduced by David Werring on page 18.

It is hard to keep up to date with the indications, efficacy and safety concerns of the new licensed therapies for early relapsing remitting multiple sclerosis. Lilia Dimitrov and Ben Turner from Barts, London, write the first of their three articles on the state of play of oral therapy in multiple sclerosis – in this article giving us an account of fingolimod.

Finally, Jane Anderson, from Cambridge, writes on migrainous vertigo, its mimics and the pitfalls in the diagnosis, in Anish Bahra's headache series. This is a clear and helpful article that covers well a common clinical problem.

We have our usual conference, journal and book reviews, plus a case report, and hope you enjoy this issue of ACNR and the summer.

Mike Zandi, Editor.
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Half a tablet of Olena can be given for a dose of 10mg.

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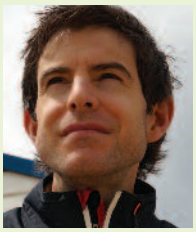
PRESCRIBING INFORMATION: Olena 20mg Dispersible Tablets Fluoxetine hydrochloride. **Presentation:** Each dispersible tablet contains fluoxetine hydrochloride equivalent to 20mg fluoxetine. **Indications:** *Adults:* Major depressive episodes, obsessive-compulsive disorder and bulimia nervosa. *Children and adolescents aged 8 years and above:* Moderate to severe major depressive episode. **Dosage and administration:** For oral administration. *Adults and Elderly:* The recommended dose is 20mg daily which may be increased gradually to a maximum of 60mg. Caution is recommended when increasing the dose in elderly. *Children:* The starting dose is 10mg/day given as half of a tablet. Abrupt discontinuation should be avoided and the dose should be gradually reduced. **Contraindications:** Hypersensitivity to any of the components. Combination of fluoxetine with MAOIs. **Precautions and warnings:** Caution should be exercised when used in children and adolescents under 18 years of age, seizures, mania. Lower dose is recommended in patients with hepatic dysfunction. Patients with cardiovascular effects, fructose intolerance and patients taking St. John's wort should be cautious. An adjustment of dose is recommended in patients experiencing weight loss, diabetes, suicide/suicidal thoughts, haemorrhage and mydriasis. **Interactions:** Serotonergic drugs, phenytoin, lithium, tryptophan, CYP2D6 isoenzymes, oral anticoagulants, alcohol and other SSRIs. **Pregnancy and lactation:** Fluoxetine can be used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour. Increased risk of cardiovascular defects when used in first trimester. It is known to be excreted in human breast milk. **Undesirable effects:** *Common:* Headache, nausea, insomnia, fatigue, diarrhoea, anxiety, nervousness, restlessness, tension, libido decreased, sleep disorder, abnormal dreams, disturbance in attention, dizziness, lethargy, somnolence, tremor, vomiting, dyspepsia, dry mouth, palpitation, QT prolongation, cardiac arrhythmias, flushing and blurred vision, oesophageal pain, hypotension and increased risk of bone fractures in patients receiving SSRIs and TCAs. (Please refer Summary of Product Characteristics for detailed information). **Overdose:** Symptoms of overdose include nausea, vomiting, seizures, cardiovascular dysfunction and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare. **Legal category:** POM. **Basic NHS cost:** £3.44 for 28 x 20mg. **Marketing authorisation Number:** PL 12762/0475. **Marketing Authorisation Holder:** Amdipharm Mercury Company Limited (AMCo), 1st Floor, Capital House, 85 King William Street, London, EC4N 7BL. **Date of preparation:** October 2013. **Date of revision:** December 2013.

Adverse events should be reported to the local regulatory authority. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Amdipharm Mercury Medical Information via telephone on 08700 70 30 33 or via e-mail at medicalinformation@amcolimited.com.

UK/OLE/AD/105B/2014 Date of preparation: June 2014

Disease-modifying therapy trials in PD: what are the issues?



Jonathan Evans
is a Specialist Registrar in Neurology at the Norfolk and Norwich Hospital. His PhD was in the field of natural history modelling in Parkinson's disease and his current research interest is in clinical trials in neurodegenerative disorders, particularly outcome measure development.

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Summary

- There is a major unmet need for therapies that slow or stop neuronal cell death in neurodegenerative disorders including PD. Conventional methods of developing new therapies are expensive and have yielded little
- Innovations in trial design such as the use of re-purposed therapies in studies with multiple arms show much promise
- Better modeling of PD progression through Natural History studies will contribute to improved trial design

The search for therapies capable of modifying, slowing or stopping neuronal cell death in neurodegenerative disorders remains elusive. In Parkinson's disease (PD) a range of agents have been studied as potential disease-modifying therapies (DMTs), including oral agents, and neurotrophic factors and gene-transfection therapies delivered directly to the striatum. Transplants of tissue derived from foetal ventral mesencephalon have also been used with variable outcomes (reviewed in reference 1). It is envisaged that a better understanding of cellular re-programming events will soon herald an exciting new era of cell-based therapies for PD, with disease-modification becoming a realistic proposition.

However, studying DMT effects in PD is far from straightforward. Historically, the promise shown by many agents in phase II trials has not translated into benefits in larger phase III studies. Fundamental flaws in the design of these trials has contributed to this failure rate. In this article I outline the issues which we face in conducting trials of DMTs with particular reference to PD, and explore how innovations in clinical trial conduct and design might aid our evaluation of this exciting new generation of therapies.

Selection of candidate therapies for DMT trials

The conventional approach to developing a novel therapy is summarised in Figure 1. There are three main stages: Discovery (target identification, identification of lead compounds through screening, optimisation of lead compound), preclinical evaluation (pharmacological efficacy, evaluation of toxicology and interactions) and clinical development (phase I, II and III trials). Whilst this approach appeals to the scientific rationalist in us, it is time-consuming and costly and has yielded few if any successes in Neurology, and none in the area of DMT.

Alternative strategies must be considered. The re-purposing or re-positioning of drugs already approved in other indications is an increasingly popular approach.[2] The principle is that biological active compounds approved in other indications may have additional 'off-target' effects, including neuroprotective effects. By focusing upon agents with existing regulatory approval and safety data we can circumvent some of the cost and time constraints associated with drug development, and in some fields the success rates for re-positioned drugs approaches 30%.[3]

Trials of re-positioned drugs are already taking place in Neurology. Dimethyl Fumarate and, more recently, Simvastatin have shown effects in Multiple Sclerosis.[4,5] In PD, a number of such studies are ongoing (reviewed in reference 6). Exenatide, originally developed as an anti-diabetic drug, has been reported to show DMT properties in a small, open-label 'learning trial'.[7] On the strength of such studies collaborative initiatives to advise on and co-ordinate learning trials of re-purposed agents have been formed.[6] Selection of appropriate candidates is the most critical and difficult aspect: criteria such as an ability to penetrate the blood-brain barrier, effects in animal models and a proposed mode of action which accords with current understanding of PD pathogenesis could all reasonably be used. Scientifically this approach is less satisfying; the links with insights from basic science are weakened and, to an extent, it is hypothesis-generating rather than hypothesis-testing. Putative pathogenic mechanisms are invoked after the fact to explain observations, although it is plausible that useful insights into neurodegenerative mechanisms may be uncovered.

Trial Design

Given that the natural history of treated PD typically runs for many years, trials of putative neuroprotective agents are likely to involve lengthy follow-up periods in large sample groups. The costs of running such trials is considerable, but could be mitigated, for example, by applying futility designs in pilot studies using smaller sample sizes, screening out therapies which are unlikely to prove effective. Futility designs typically involve the comparison of a single treatment arm with a pre-determined lower limit of success (or an upper limit for worsening) in a one-sample test.[8] Therapies performing above criterion can then be selected for larger, phase III studies ("seamless" transition). Multiple futility studies can be run in parallel (multi-arm or nested designs), including arms using combinations of therapies (Figure 2). Should one or more arms close, participants can be moved to alternative arms (adaptive design). Efficient trial designs reduce turnaround time and trial costs.

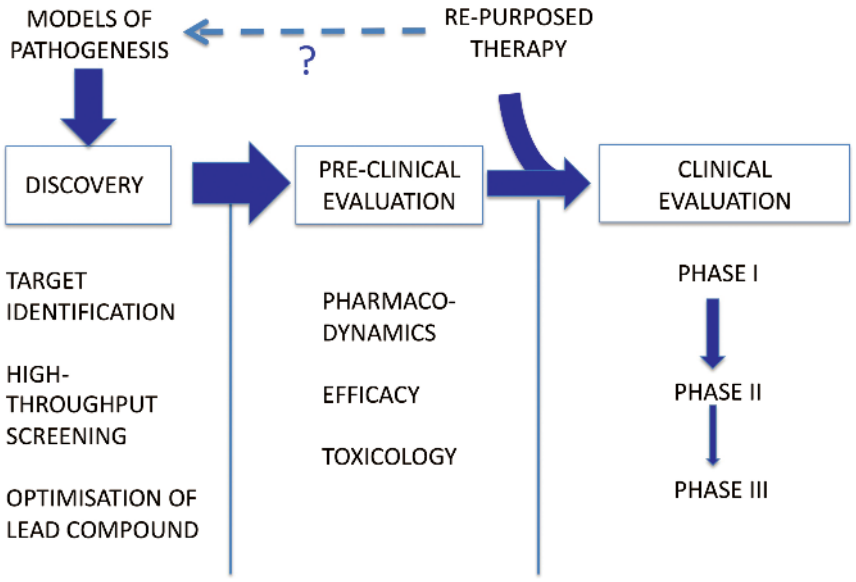

Figure 1: Stages of drug development, modified to illustrate how a re-purposed therapy can enter the process at a later stage, achieving a cost and time saving. Arrow sizes are drawn so as to denote drop out of candidate agents over the development cycle. Re-purposed therapies proven to be effective in a new indication may provide a posteriori insights into disease pathogenesis.

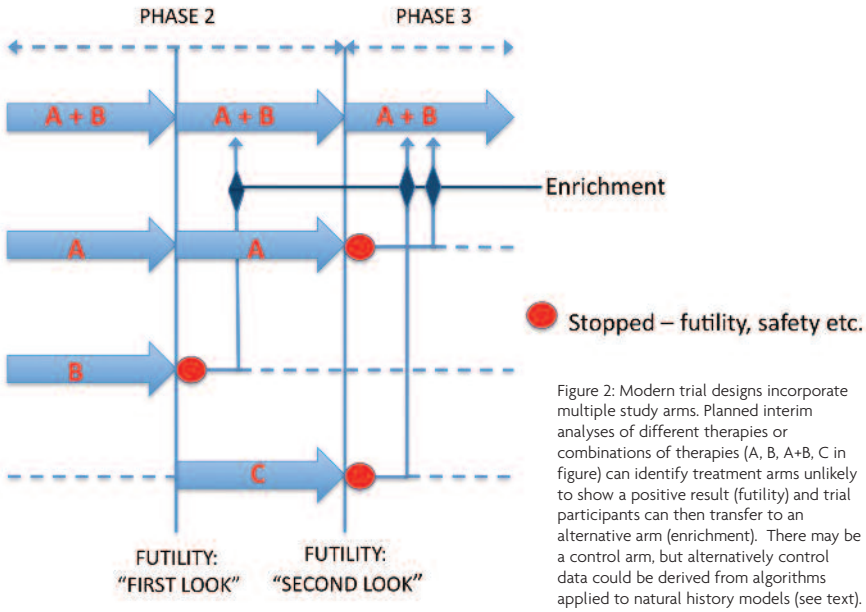

Figure 2: Modern trial designs incorporate multiple study arms. Planned interim analyses of different therapies or combinations of therapies (A, B, A+B, C in figure) can identify treatment arms unlikely to show a positive result (futility) and trial participants can then transfer to an alternative arm (enrichment). There may be a control arm, but alternatively control data could be derived from algorithms applied to natural history models (see text).

One problem inherent in the application of futility designs to the study of DMTs in neurodegeneration is that such a design assumes that the absence of short-term efficacy precludes long-term efficacy. Theoretically, an agent modifying neuronal cell death signals may show a slowly developing benefit or a 'lag-benefit' and may be screened out in a futility trial. We are faced with a Catch-22, as extending the follow-up periods in futility trials defeats their original purpose! Simple pragmatism, then, must prevail. Detection of a clinically meaningful effect in fewer than 6 months is largely implausible, and an agent showing no efficacy after 18 months is unlikely to thereafter, Thus a time frame of 6-18 months would be reasonable for pilot DMT studies, with the caveat that agents suspected a priori to have delayed benefits are less suitable for such futility trials. Detection of relevant effects over such a time-frame would be facilitated by the inclusion of subjects at risk of more rapid disease progression, such as those older at disease onset. In the future, genotyping for genetic polymorphisms that influence disease progression, as has been described for the glucocerebrosidase[9] should further assist with stratification of trial subjects. DMTs in neurodegenerative disorders should be most effective when employed early in the disease course and this must also inform the inclusion criteria used in these studies.

Separation of symptomatic and DMT effects

Identifying the optimum outcome measures for trials of putative neuroprotective agents in PD is far from straightforward. Biomarkers of progression, such as those derived from imaging, have been used but are insensitive measures of neurodegeneration.[10] Commonly used clinimetric rating scales, such as the Unified Parkinson's disease Rating Scale part III (UPDRS-3) are capable of capturing long-term changes over time, but do not measure all aspects of neurodegeneration.[11] Furthermore, any putative neuroprotective agent which augments dopaminergic function may produce concurrent symptomatic benefits which cannot easily be disentangled from true disease-modification. We have previously proposed the use of alternative outcome measures, such as time to significant, irreversible disease milestones (loss of postural reflexes, dementia).[12] This would, of course, necessitate extended periods of follow-up. In this regard, improving our understanding of the natural history of treated PD would be highly beneficial. Theoretically, the observed progression of trial participants on a given index could be tracked against their expected disease trajectory derived from an individualised natural history model. Such an approach would allow us to separate important DMT effects more easily, and might ultimately obviate the need for separate control arms.

The use of clinimetric rating scales introduces a further issue, namely the extent to which objective responses on such scales translate into day-to-day benefits for patients. As clinicians, instinctively we hone in on p-values, in so-doing prioritising [statistically] significant differences ahead of clinically important differences. The Minimal Clinical Difference (MCD) is the minimum change on a scale which can be recognised by a rater/experienced by a patient. For the UPDRS-3, the MCD is approximately 2.5.[13] For reference, in the ADAGIO Study using rasagline, the mean difference between early- and delayed-start arms at 72 weeks was <2 points on the UPDRS-Total.[14]

Related to this is the need to ensure DMT trials are powered appropriately. A priori sample size calculations require an estimate of the anticipated effect size, which may be unknowable. An alternative strategy would be to accept a consensus MCD and base power calculations upon this. It is also necessary to allow for the fact that 'early looks' at the data – as would be required in nested or futility designs – reduce statistical power.

The placebo and "less-ebo" effects in PD trials

It has been suggested that the placebo effect is more powerful in PD than in other disorders.[15] There may be an additional confounder that we need to consider in PD: the so-called 'lessebo' effect. This term describes a phenomena that emerged from a meta-

analysis of RCTS of dopamine agonists conducted by Mestre et al.[16] The magnitude of the benefit of active drug (UPDRS-3 improvement) was reduced in studies that employed a placebo arm. In other words, if participants knew there was a chance of being assigned to placebo, the benefit of the active drug was reduced. Furthermore, the size of this 'lessebo' effect was proportional to the prior odds of being assigned to placebo. The use of control information derived from natural history models rather than employing a conventional control arm would be one method to reduce the effect of this potential confounder.

Conclusions

This review, though by no means comprehensive, has highlighted the important challenges facing clinical trials of DMTs in PD, and by extension other neurodegenerative disorders. Perhaps the neurological community needs to set aside certain scientific prejudices. The selection of agents based on their ability to engage particular targets is inefficient and, I would argue, we must be more pragmatic in our approach. High throughput screening of compounds for DMT effects, including repurposed therapies, must take advantage of modern trial design innovations. Improved biomarkers of true disease progression should be sought and utilised, and better models of the natural evolution of the disorder with time must inform our selection of meaningful and relevant outcome measures for DMT trials.

This is an exciting era in PD therapeutics: International initiatives such as the cell-transplantation programme TransEuro serve testament to this.[17] Proving the benefits of novel DMTs will require a systematic approach to clinical trial design. This remains a considerable challenge, but one which we are increasingly able to meet. ◆

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Oral therapies in relapsing remitting multiple sclerosis – Part 1

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For some years disease modifying treatments (DMTs) for relapsing remitting multiple sclerosis (RRMS) have been limited to 'injectable' therapies consisting of just two classes of drugs, beta interferon (IFN-b) and glatiramer acetate (GA). It is recognised that IFN-b and GA have limited efficacy and tolerability.[1-2] The development of natalizumab has provided a treatment of greater efficacy but by NICE criteria is limited to those with rapidly evolving severe relapsing remitting multiple sclerosis (RES RRMS).[3] There are now three oral DMTs for RRMS licenced by the European Medical Agency (EMA), two with full published NICE guidance (fingolimod and teriflunomide), and one (dimethyl fumarate [DMF]) anticipated in summer of 2014. In addition, in the new NHS structure, specialist prescribing for MS is currently the remit of NHS England and therefore more specific guidance has been seen and is likely to come from this body.

Aside from the obvious attraction of a 'pill' for MS therapy, the increase in the options of DMTs, with different mechanisms of action and ranges of efficacy and side effects, all help in the goal of successful MS disease suppression. Clinicians now need to evaluate licencing, regulatory guidance, safety, side effects, and efficacy of the various DMTs available. This is the first of three articles which review the oral therapies, fingolimod, teriflunomide and DMF, to help the Neurologist guide patients through the 'tyranny of choice'.

Fingolimod

Current Approval

Fingolimod (Gilenya™) became the first oral therapy to be approved for the treatment of RRMS in 2010 by the USA. The European community following suit in 2011 when the EMA recommended fingolimod in patients with high disease activity despite IFN-b therapy, or rapidly evolving severe RRMS (RES RRMS). As of April 2012, NICE have recommended fingolimod for adults with RRMS who have been exposed to IFN-b with unchanged or ongoing relapse activity.[4] NHS England has now clarified that GA (Copaxone™) is considered an equivalent of IFN-b and therefore patients who have had an adequate course of GA, but on-going disease activity are eligible for fingolimod, thus resolving an outstanding discrepancy. Our understanding is the EMA licence for fingolimod will be amended to be patients with high disease activity despite full and adequate treatment (considered 12 months of treatment) with at least one disease modifying therapy, ie those who have had at least a single relapse in 12 months whilst on any DMT and with 9 T2 lesions (in total) or 1 or more new gadolinium enhancing lesions.

More recently NHS England has provided criteria of positive JC virus serology, previous immunosuppressant therapy or two years of natalizumab therapy as justification for switching from natalizumab to fingolimod.

Fingolimod is taken as single tablet once daily at a dose of 0.5mg.

Mechanism of Action

Fingolimod is a pro-drug that is rapidly phosphorylated by sphingosine kinase 2 to the active metabolite sphingosine phosphate. Sphingosine phosphate is a functional antagonist of the sphingosine 1–phosphate (S1P) receptor subtypes 1, 3, 4 and 5 that are present on lymphocytes and various cells types of the CNS and other tissues.[5] The mechanism of action of fingolimod is believed to be two-fold. Firstly it inhibits the ability of specific lymphocytes to leave lymph nodes causing a reduction in peripheral blood lymphocytes and their reduced migration into the CNS.[6] Secondly, fingolimod is able to cross the BBB and may have direct effects on the CNS with evidence of reduced axonal damage, demyelination and astrogliosis.[7]

Fingolimod is absorbed slowly, taking 12-16 hours to reach a maximum concentration and the half-life is 6 to 9 days.[8] The bioavailability is unaffected by ingestion of food.[9] Fingolimod is primarily metabolised by cytochrome (CYP)4F2 but also via reversible phosphorylation and transformation by dihydroceramide synthase.[10] Elimination is predominately via excretion of inactive metabolites in the urine (81%) with 2.5% of fingolimod and fingolimod phosphate excreted in the faeces.[8]

Clinical Efficacy

FREEDOMS, FREEDOMS II and TRANSFORMS are the pivotal Phase III trials that investigated the clinical efficacy of fingolimod.[11-13] All three trials included over 1000 patients and were multicentre, double-blind and randomised. FREEDOMS and FREEDOMS II had placebo arms and a study duration of 24 months whilst TRANSFORMS had IFN-b once weekly 30µg intramuscular (IM) injections (AVONEX™) as an active comparator and was shorter at 12 months. In all three trials fingolimod was given as a once daily dose of 0.5mg or 1.25mg however during the FREEDOMS II study, the participants in the 1.25mg arm were incorporated into the 0.5mg arm following a risk-benefit analysis. Only data for the licensed 0.5mg dose will be reviewed here (Table 2).

The primary end point of FREEDOMS, ARR, was significantly reduced by 54% for the fingolimod group compared to placebo (0.18 versus 0.40, p <

Table 1: Information about the study population across the Phase III clinical trials looking at the 3 oral MS therapeutics (dimethylfumarate, teriflunomide and fingolimod).

Drug	Study	Number (N)	Age (years)	EDSS	Recent MS history	MS classification
Dimethyl fumarate (DMF/ BG-12)	DEFINE	1234	18 -56	0- 5	1 clinically documented relapse within 12 months or 1 gadolinium enhancing lesion within 6 weeks before randomisation	RRMS
	CONFIRM	1417	18-55	0 - 5	1 clinically documented relapsed within 12 months or 1 gadolinium enhancing lesion within 6 weeks before randomisation	RRMS
Fingolimod	FREEDOMS	1272	18-55	0 - 5.5	≥ 1 relapse within the last 12 months or ≥ 2 within the last 2 years	RRMS
	FREEDOMS II	1083	18-55	0 - 5.5	≥ 1 relapse within the last 12 months or ≥ 2 within the last 2 years	RRMS
	TRANSFORMS	1292	18-55	0 - 5.5	≥ 1 relapse within the last 12 months or ≥ 2 within the last 2 years	RRMS
Teriflunomide	TEMSO	1088	18-55	0-5.5	1 relapse in the past 12 months or 2 in the past 24 months but none in 60 days before randomisation	RMS*
	TOWER	1169	18-55	0-5.5	1 relapse in the past 12 months or 2 in the past 24 months but none in 30 days before randomisation	RMS
	TENERE	324	≥ 18 years	0-5.5	No relapse in 30 days prior to study	RMS

*RMS: relapsing multiple sclerosis: This includes RRMS but also progressive forms of MS that have relapses (secondary progessive MS and progressive-relapsing MS)

Table 2: Summary of 0.5 mg fingolimod efficacy across Phase III clinical trials

Clinical outcome	FREEDOMS (n = 1272, 24 months)		FREEDOMS II (n = 1083, 24 months)		TRANSFORMS (n = 1292 , 12 months)	
	Fingolimod 0.5mg	Placebo	Fingolimod 0.5 mg	Placebo	Fingolimod 0.5mg	IFN-b
Annualised relapse rate - p value	0.18 <0.001	0.40 –	0.21 <0.001	0.40 NA	0.16 <0.001	0.33 NA
Cumulative probability of disability progression confirmed at 3 months during study (%) - p value	17.7 0.03	24.1 NA	25.3 0.32	29 NA	NA	NA
Mean no. Gd+ lesions at 24 months - p value	0.2 <0.001	1.1 NA	0.37	1.22	0.23 0.004	0.51 NA
Mean no. of new or newly enlarging T2 lesions - p value	2.5 <0.001	9.8 NA	2.3 <0.001	8.9 NA	1.7 <0.01	2.6 NA
Mean brain volume change (%) - p value	-0.84 <0.001	-1.31 NA	-0.86 <0.001	-1.28 NA	-0.31 <0.001	-0.45 NA

0.001).[11] Fingolimod also reduced the risk of disability progression confirmed at three months by 30% and at six months by 37%. MRI investigations performed at 24 months showed 82% fewer gadolinium-enhancing lesions compared to the placebo arm (0.2 versus 1.1, p < 0.001) with a greater proportion of patients free from gadolinium-enhancing lesions in the fingolimod arm (89.7% versus 65.1%). There were also fewer new or enlarging T2 lesions (2.5 versus 9.8, p <0.001) and again a greater proportion taking fingolimod showed no new or enlarging T2-weighted lesions at 24 months compared to those on placebo (50.5% versus 21.2%, p <0.001). The atrophy data for fingolimod was also very promising with 35% less brain atrophy compared to placebo over the course of the trial (-0.84% versus -1.31%, p <0.001).

FREEDOMS II incorporated safety recommendations made by the FDA following FREEDOMS.[12] Again, fingolimod significantly reduced ARR compared to placebo, this time by 48% (0.21 versus 0.40, p <0.0001). Disappointingly there was no difference in the second primary endpoint of disability progression. Data from imaging showed that those in the fingolimod group had significantly fewer gadolinium-enhancing lesions compared to placebo (0.37 versus 1.22, p <0.0001) and this finding was mirrored in the number of new/ enlarging T2 lesions (2.3 versus 8.9, p <0.0001). A similar result as seen in FREEDOMS was found for brain volume loss, with 33% less brain atrophy in fingolimod arm compared to placebo (-0.858% versus -1.279%, p <0.0002).

In TRANSFORMS, ARR was reduced by 52% in those taking fingolimod compared to IFN-b (0.16 versus 0.33, p <0.001).[13] As may be expected in such a short trial there was no statistically significant difference in disability progression over the course of the study between fingolimod and IFN-b. There was however a 35% reduction in new or enlarging T2 lesions on MRI compared to IFN-b (p=0.004) and fewer mean gadolinium enhancing lesions (0.23 versus 0.51, p < 0.01). Brain atrophy data was also favourable with 33% less brain volume loss compared to the IFN-b (-0.31 versus-0.45 respectively p < 0.001).

Safety

Fingolimod has been studied in four major clinical trials and combined with postmarketing surveillance this amounts to more than 135,800 patient years.[14] There were three deaths in FREEDOMS, only one of which was in the fingolimod arm (unlicensed 1.25mg dose) due to suicide.[11] Two deaths occurred in TRANSFORMS, again both in the 1.25mg group; the first from disseminated primary varicella zoster who was taking concommitant steroids and the second from herpes simplex encephalitis.[13]

Adverse events occurred at a similar frequency between the 0.5mg and placebo arms in FREEDOMS, whereas they were more commonly seen in those taking IFN-b in TRANSFORMS (91.6% versus 86%, IFN-b and fingolimod 0.5mg arms respectively). Serious adverse events interestingly were higher in those receiving placebo (13.4%), than fingolimod 0.5mg (10.1%) in FREEDOMS.[11]

Pooled analysis across all three studies showed a higher incidence of bradycardia in the fingolimod arm compared to placebo (1% versus 0.6%).[15] Bradycardia generally began after the first hour of taking the first dose, reached a peak four to five hours later and was asymptomatic. It is known that sphingosine-1 phosphate has direct effects on the pacemaker activity of the sino-atrial node.[16] Systolic blood pressure across FREEDOMS rose modestly by 1.9mmHg and diastolic by 0.7mmHg in those treated with 0.5mg fingolimod.[11]

Unsurprisingly peripheral blood tests showed leucopenia (primarily lymphopenia). This is reversible with return to pre-medication levels some 8 to 16 weeks after cessation of fingolimod. Herpes infections, bronchitis and pneumonia occured more frequently in those taking fingolimod across all major studies.[15] However overall infection rates were similar, with infection occurring in 67.9% of those on placebo versus 65.1% of those taking fingolimod 0.5mg, with no single infection correlating with lymphocyte count.[15,17]

Macular oedema occurred in 0.4% on fingolimod 0.5mg compared to 0.1% for placebo, generally three to four months after starting treatment.[15] This is likely to be due to endothelial effects compromising the blood-retina barrier.[18] Those with a history of diabetes and or uveitis appear to be particularly at risk.[19]

Reduced pulmonary function has also been observed in those taking fingolimod, with an average reduction in FEV1 of 3.1% and DLCO of 3.8% after 24 months (compared to 2% and 2.7% respectively in placebo).[19]

As seen in the other treatments discussed here, fingolimod is also associated with dysfunctional liver enzymes with more frequent cases of three-fold increases in liver enzymes in those taking 0.5mg compared to placebo and IFN-b (8.3% versus 1.8% versus 2.9% respectively).[19] Liver function tests appear to return to baseline following treatment discontinuation.

Animal data suggests that fingolimod is teratogenic. 219 pregnancies have been reported in participants of the trials with 8/67 live births born with congenital abnormalities.[20] Fertile female patients should be advised to take effective contraception until two months after treatment termination due to the time taken to eliminate fingolimod from the body.

Adverse events leading to discontinuation of study drug in FREEDOMS were equal at 8% in both the 0.5mg and placebo arms.[11] Data from TRANSFORMS also had similar results with only 5.6% of those taking 0.5mg fingolimod and 3.7% of those on IFN-b discontinuing due to adverse effects.[13] ◆

Monitoring recommendation for fingolimod

Before treatment

Full blood count at baseline

Varicella zoster immunity should be checked, if there is no evidence of VZV Ig then vaccinate for VZV

Ophthalmology review prior to treatment commencement in those patients with the aforementioned risk factors

During treatment

Medical supervision for the first 6 hours after the first dose is taken with an initial and repeat ECG at the end of the supervision period

Assessments of FBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count ‹0.2x109/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count ‹0.2x109/l..

Liver transaminases at 1, 3, 6, 9 and 12 months then periodically thereafter. If rises › 5 x ULN then more frequent monitoring required and inclusion of alkaline phosphatase and bilirubin.

Ophthalmology review is recommended at 3-4 months. At risk groups require additional review during treatment.

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Migraine and vestibular dysfunction

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Summary

- Vestibular symptoms in migraine are disabling and may be the dominant feature leading to inaccurate diagnosis
- Recurrent episodic vertigo is common in migraineurs and most frequently due to the migraine process itself
- Co-morbid peripheral vestibular disorders occur at higher prevalence in migraineurs
- Vestibular dysfunction can be a trigger in migraine and needs due recognition
- Vestibular migraine is the chameleon to spot as the drive is migrainous but the course of vertigo is highly variable in duration, attack frequency and association with cephalagia- with the latter not infrequently attenuated. For pointers to identifying the vestibular dysfunction see Table 1.

The association of vestibular aura/dysfunction with migraine is often under-recognised leading to delayed treatment, adding further to the burden of disability migraineurs suffer. Migraine is one of the commonest neurological complaints with a lifetime prevalence of 16%, with headache representing one fifth of neurology outpatient referrals.[1] It is recognised by WHO to be ranked amongst the top 10 most disabling conditions with psychiatric morbidity at the top of the league table. Vertigo is also extremely common with a life-time prevalence in adulthood of 7%, having a significant psycho-social impact. Migraineurs are more likely to suffer from vertigo with 3.2% affected and this is in excess of the anticipated co-morbid prevalence of 1.1%.[2] This cohort of migraineurs with vestibular dysfunction, have significant associated psychiatric morbidity with the highest indices of anxiety reported in vertiginous cohorts with vestibular migraine.[3]

Whilst cephalgia is typically the most prominent complaint, vestibular disturbance can predominate as part of an aura presentation – brainstem aura – or through parallel dysfunction in vestibular pathways – vestibular migraine – or as co-morbid vestibular disorders such as BPPV and Meniere's. Discriminating between the centrally driven migrainous process and peripheral lesions is important to tailor treatments and direct management.

Common vestibular disorders in migraine

Recurrent vertigo is most common in migraineurs and although this is frequently migrainous in origin, the high prevalence of vestibular disorders raises the question of overlapping pathophysiology.

Benign Paroxysmal Positional Vertigo (BPPV):

Transient vertigo due to BPPV is common, with attacks typically lasting seconds and recurring over several weeks but usually self-limiting. It is triggered by specific changes in the position of the head and is caused by the movement of displaced otolith crystals within the semi-circular canals. In tertiary neuro-otology clinics BPPV is one of the most common underlying diagnoses; accounting for a fifth of cases in the 5000 cases reviewed at the Munich centre.[4] In those with idiopathic BPPV they are however twice as likely to have co-morbid migraine.[5] BPPV in this patient group needs to be independently treated with canalith repositioning manoeuvres, particularly given that the vestibular presentation may serve as a trigger for migraine.

Meniere's Disease:

The differentiation between Meniere's and migraine in a single acute vertiginous attack with emesis and headache is often difficult. However repeated attacks allow for discrimination of Meniere's: with audiometrically evident hearing loss (typically unilateral although can become bilateral over time, rarely alternating between ears) and horizontal nystagmus which may initially only be manifest during the attack. In addition to profound vertigo lasting typically in excess of 20 minutes, report of tinnitus or aural fullness together with progressive hearing loss is diagnostic.[4] The condition is driven by endolymphatic hydrops with paraclinical supporting evidence of significant audiological loss and peripheral vestibular dysfunction on oculographic calorics. Once again migraine is twice as common in this group[6] and with audiological loss fluctuating it may not be captured on pre-arranged testing in the early stages and testing at the time of the attack should be pursued if there is any doubt. Treatment for Meniere's includes a low salt diet, diuretics and high dose betahistine.

The relationship between migraine and Meniere's remains unclear however a causal relationship has been questioned following the observation that those with migraine develop Meniere's earlier and more frequently have bilateral hearing loss.[7]

Migraine in association with vestibular symptoms

Two migraine phenotypes are recognised in the international classification of headache disorders (ICHD version 3 beta:[8]) with prominent vestibular symptoms: Migraine with brainstem aura and Vestibular migraine.

Migraine with brainstem aura

Having previously been called basilar artery migraine in reference to the presumed unifying

Table 1: Summary of vestibular dysfunction seen in migraine

	Typical duration of attack	Pattern of presentation	Triggers	Tests to consider	Specific treatments
BPPV	secs to mins	recurrent over weeks; fatigable	Head position	Epley Vestibular	Canalith repositioning manoeuvres
Meniere's disease	>20mins -24hrs	episodes often with prolonged inter-ictal periods (mths)	?high salt diet ?migraine	Audio-vestibular	Diuretics Low salt diet Betahistine
Motion sickness	Prolonged >30mins - hrs	triggered	Motion Visual perception of movement	Nil	Anti-emetics
Migraine with brainstem aura	<60mins	episodic to chronic	Migraine triggers: – stress – menstruation – sleep architecture – diet & dehydration – alcohol – exercise – weather	MRI	Anti-migraine including anti-epileptics, pizotifen and flunarazine
Vestibular migraine	Variable: secs, mins, hrs	episodic to chronic		Audio-vestibular	Role for customised vestibular rehabilitation once cephalgia is suitably controlled.
	recurrent	Vestibular dissociation from cephalgia common			

arterial pathophysiology, our current understanding of migraine has taken us beyond a primary vascular aetiology (as outlined by Holland and Afridi, ACNR 2014;V13(7):19-21) and this is recognised by the ICHD in renaming this as migraine with brainstem aura. Whilst vestibular dysfunction may occur in this phenotype, in association with other brainstem aura phenomena, its presence is in keeping with aura and as such the duration of the vertiginous attack is consistent with that of Leao's cortical spreading depression lasting one hour. Two or more brainstem mediated phenomena evolving or occurring in succession over more than five minutes include: vertigo, tinnitus, hypoacusis, diplopia, bilateral visual symptoms, simultaneous bilateral sensory paraesthesia, ataxia, loss of consciousness. This is in conjunction with migrainous unilateral, throbbing, moderate to severe headache, starting during or within one hour of the aura and lasting more than four hours with hypersensitivity to external sensory stimuli (photophobia, phonophobia, osmophobia) and typical aggravation on routine physical activity. Please refer to Box 1 for summary of ICHD3beta diagnostic criteria for migraine with brainstem aura.

Migraine with brainstem aura is rare in both migraine and neuro-otology, occurring in 10% of those with migraine with aura.[9]

Vestibular migraine

Vestibular migraine with vestibular symptoms in isolation of other brainstem aura is much more common accounting for up to 10% of patients seen in tertiary neuro-otology dizzy clinics.[4] Please refer to box 2 which details the ICHD3beta diagnostic criteria for vestibular migraine. Importantly the duration of vertigo can be very variable and in up to 70% is not in keeping with aura duration: lasting seconds, hours or days. In addition the association with cephalgia is variable with only 48% reporting consistent cephalgia although migrainous associated symptoms of phonophobia and photophobia are more prevalent. Vertigo can

Box 1: Migraine with brainstem aura (1.2.2)

Former terms: Basilar artery migraine; basilar migraine; basilar-type migraine.

Migraine with aura symptoms clearly originating from the brainstem or with evidence of bi-hemispheric involvement, but no motor weakness.

Diagnostic criteria:

At least two attacks fulfilling the following criteria:

1. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
2. At least two of the following brainstem symptoms:
   a. dysarthria
   b. vertigo
   c. tinnitus
   d. hypacusis
   e. diplopia
   f. ataxia
   g. decreased level of consciousness
3. At least two of the following characteristics:
   a. at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
   b. each individual aura symptom lasts 5-60 minutes
   c. at least one aura symptom is unilateral
   d. the aura is accompanied, or followed within 60 minutes, by headache

NB. transient ischaemic attack has been excluded.

Box 2: Vestibular Migraine (A1.6.5)

Former terms: Migraine-associated vertigo/dizziness; migraine-related vestibulopathy; migrainous vertigo

A current or past history of Migraine without aura or Migraine with aura with concurrent vestibular symptoms.

At least five episodes fulfilling the following criteria:

1. Vestibular symptoms of moderate or severe intensity, lasting between 5 minutes and 72 hours, including (as defined by the Bárány Society):

a. spontaneous vertigo:
   i. internal vertigo (false sensation of self-motion);
   ii. external vertigo (false sensation that the visual surround is spinning or flowing);

b. positional vertigo, occurring after a change of head position;

c. visually induced vertigo, triggered by a complex or large moving visual stimulus;

d. head motion-induced vertigo;

e. head motion-induced dizziness with nausea (dizziness is characterised by a sensation of disturbed spatial orientation; other forms of dizziness are currently not included in the classification of vestibular migraine).

2. At least 50% of episodes are associated with at least one of the following migrainous features:

a. headache with at least two of the following four characteristics:
   - unilateral location
   - pulsating quality
   - moderate or severe intensity
   - aggravation by routine physical activity

   b. photophobia and phonophobia

   c. visual aura

occur at any time point during the migrainous episode, with the attack frequency being highly variable with days to years between events. The average age of onset of vertiginous attacks post-dates the onset of migraine by years and migraine may have become quiescent, with the headache during the vertiginous attacks often attenuated- emphasising the utility of a directed interrogation of former migraine in those presenting with recurrent episodic vertigo.[10] Trigger factors precipitating attacks may also prove useful as the episodes are often triggered by well-established migraine triggers as detailed in the summary table. Ultimately further diagnostic clarity can be derived from the good response to treatment with anti-migraine preventatives. In clinical practise the full array of migraine preventatives are used including beta blockers, tricyclic antidepressants, anti-epileptics (topiramate, sodium valproate etc.), serotonergic (pizotifen) drugs and calcium channel blockers (flunarazine) –the latter with anecdotal significant utility. Unfortunately clinical drug trials in vestibular migraine remain either underpowered or compounded by lack of rigour in diagnostic inclusion.

Distinct from Meniere's disease, significant progressive hearing loss or vestibular deficit are not a persistent feature in vestibular migraine. The diagnosis of vestibular migraine should be based on the history as there are no diagnostic findings on examination or audio-vestibular assessment. Significant nystagmus in the migraineur should be treated with caution and a peripheral cause considered in those with otherwise normal examination and no clinical pointers to central disorders. Unilateral hypo-excitability on calorics without associated pathological nystagmus however should not raise concern as this simply indicates prior centrally compensated peripheral vestibular deficit. In both BBPV and vestibular migraine head motion precipitated vertigo occurs: in BBPV this is fatigable and self-limiting, with an abnormal examination whilst symptomatic; whilst the vertigo of vestibular migraine is recurrent, non-fatigable and with a typically normal examination when symptomatic.

Vestibular trigger to migraine

Discerning the underlying cause of vertigo in migraine is paramount as it will enable both tailored treatment and in the case of co-morbid peripheral vestibular disorders will also serve to reduce a potential migraine trigger. In a prospective study of the incidence of migraine in the 24 hour period following vestibular testing (including calorics) almost a half of migraineurs studied recorded migraine and this frequently occurred during the induced vertigo.[11] This underlies the need to carefully interrogate presentations where vertigo just precedes the onset of migraine and not assume that this is vestibular migraine.

Motion sickness

Motion sickness can be defined as prolonged symptoms of dysequilibrium in conjunction with nausea provoked by movement or the illusory perception of movement. In migraineurs, contrary to other peripheral disorders, there is a high prevalence of motion sickness with approximately two thirds affected either with an antecedent or concurrent history.[12,13] Current theories in migraine associated phenomena focus on sensory dysmodulation. It is proposed that motion sickness highlights failure of normal integration of vestibular, visual and proprioceptive cues with disruption of normal inhibitory gating mechanisms in the brainstem responsible for hypersensitivity of the emetic centre, sharing a similar underlying pathophysiology to migraine (for comprehensive review: 14). In movement induced motion sickness the principal mediator is the vestibular apparatus with experiments showing complete attenuation of this phenomenon in those without a functional vestibular apparatus. However visual induced motion sickness is not directly mediated by the vestibular apparatus but rather reflects dysmodulation of converging sensory inputs, and is more frequently seen in migraineurs compared to controls.[15] ◆

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Participating in the Prosavin Gene Trial

I have lived with Parkinson's for almost one third of my life. This life-affecting condition has challenged my ability to function in every possible way. I lost confidence, dignity and hope. For 18 years I experienced mobility problems, falls, constant pain, sleep deprivation, screaming nightmares, dyskinesia, 'freezing', and in my case, spontaneous closure of my vocal cords and being unable to breath.

I was spiraling downwards with little hope. The transition from extreme involuntary movements to completely frozen took four seconds, which meant that I was unable to get into a safe position. Often the freezing would last for up to two and half hours, and took some time to return to moving around again.

At this time I spent about 75% of each day OFF which meant that I spent long periods sitting and waiting until I came back ON again. Only 20% of my day was ON but this was blighted by involuntary movement, which made it hard to do anything, and led to a withdrawal from society to prevent me from hitting people, and because I was exhausted by the constant movement.

All of these symptoms changed me into a person that I no longer recognised. In 2010, when I was thinking that things could not get worse, they got worse. The house caught fire in the middle of the night, my husband was very ill and my horse and cat died. My PD got worse.

My medication regime at that time was Ropinerole XL 8mg, one tablet per day. Stalevo – 100mg levodopa, 25mg carbidopa, 200mg entacapone every 2 hours, Sinemet 62.5 as required, Amantidine 100mg, twice daily, Modafinil 200mg in the morning, Clonazepam 1/2mg at night and Rasagiline once daily. This medication was becoming less effective.

Sheila Roy

In February 2011 Dr Roger Barker referred me to Dr Philip Buttery, both at Addenbrooke's Hospital, to consider my suitability for deep brain stimulation. During this consultation the Prosavin study was raised. This was the first time that I heard about ProSavin. Dr Buttery said that they were looking for three people to take part in assessing the safety, efficacy and dose evaluation of Prosavin in people with mid-stage Parkinson's, who were experiencing reduced benefit on levodopa medication. The study evaluated three dose levels in a total of 15 patients with PD. Six people received the higher 5x dose, and I was one of these.

As soon as I heard about the study on ProSavin I knew it was for me. I felt very confident that, if possible, I should go for it. A lot of people tried to persuade me otherwise, but I felt that it was right for me. I cannot say that this has been an easy process. I have to watch my body for involuntary movement, and reduce my intake of Dopamine. This has been hard to do, and gets harder the more I reduce. It is not a gradual incline but like a step up in response to dyskinetic movements. It has taken me two years to reduce from ten Stalevo tabets a day, to five. I am not cured. I still have involuntary movement, and OFF/ON times but they are not as severe as they were, and I know when they are coming, and can function when OFF.

My mobility is much improved, but for me the most important thing is my ability to think, analyse and articulate. I could not hold a good conversation a year ago, and now I can. I had a lot of falls and now I rarely fall. I can write, which I love and I laugh a lot.

I now have a little factory in my brain that produces dopamine. I have a much better sleep pattern than I used to. I used to only get about 3 hours sleep in 24 hours – now I'm getting around 7 hours which has made a tremendous difference and it means that my body has more chance to heal, and you feel better if you get some sleep. I still get terrible nightmares and nothing seems to make that any better. I scream the house down and I warn visitors that not only do I wander around all night but I scream. We're not the best people to stay with!

I have an increase in ON time – the time when I'm fully functional. I've gone from four hours to eleven hours a day – so most of my day is active and it makes such a difference. You just have more time to enjoy yourself and to do things and you're not falling asleep all the time or doing things that stop you enjoying yourself.

I've got a much improved mood. I think I spent a lot of 2010-2011 crying. It's an unbelievable feeling – you're just so miserable all the time. But my mood has really picked up and I'm much more sociable. I'm much more confident than I was. I came to the point where I couldn't go out into a crowd. I couldn't function at all talking to people – I was completely unable to communicate and I just stayed at home. I just was going downhill fast, as everything wasn't functioning anymore. So it's a big change.

With Parkinson's you tend to be going downwards not up. Since starting this study I've felt I have improved and I'm really encouraged by that. It means that that it is possible to turn this condition around. Let us hope so.

One question that you should be asking me is 'would I do it again?' – and I would, I'd do it again tomorrow. Because for me it's made a big, big difference to my life. ◆

"I have an increase in ON time – the time when I'm fully functional. I've gone from four hours to eleven hours a day – so most of my day is active and it makes such a difference"

Should patients with early morning akinesia have an apomorphine injection as their first daily dose?

Highlights of a debate held at the 8th World Congress on Controversies in Neurology (CONy), 9th May 2014, Berlin, Germany

Key points

- **Morning akinesia due to delayed time to ON (TTO) following the first levodopa dose is a common and debilitating symptom in PD, occurring across all stages of disease and in around 60% of patients**
- **Gastroparesis is a major factor in delayed TTO of a levodopa dose**
- **Many strategies for the management of morning akinesia while decreasing the severity of the OFF state do not improve TTO**
- **Subcutaneous apomorphine injection bypasses the GI route and interim results of the AM IMPAKT study show that it provides rapid and reliable TTO in PD patients with morning akinesia and a significant improvement in their quality of life**

Morning akinesia is a common but under-recognised symptom in patients with Parkinson's disease (PD) and results from a delay in time to ON (TTO) of the first daily dose of levodopa. Studies have shown that early morning OFF periods are frequent across all stages of PD, occurring in almost 60% of patients [1]. As a consequence, a large proportion of PD patients are likely to have difficulties starting their day due to debilitating motor and non-motor symptoms. Despite its reported frequency, the recognition and effective management of morning akinesia appears to be suboptimal and so at the 8th CONy Congress in Berlin, an international faculty met to debate the best treatment options to ensure that patients achieved an ON state upon awakening.

Over time, OFF periods, including morning akinesia, develop in PD patients treated with levodopa and while these have traditionally been considered as due to end-of-dose wearing off, more recently delayed TTO has been recognised as a significant contributor to total OFF time [2]. OFF periods can occur despite optimised oral therapy which impacts the patient's daily routine and reduces their quality of life (QoL) [3, 4].

Professor Stuart Isaacson (Associate Professor, Florida International University School of Medicine, Florida, USA) highlighted the fact that gastrointestinal (GI) dysfunction, including gastroparesis (delayed gastric emptying), is a common feature of PD. In addition to causing GI symptoms, such as nausea and bloating, gastroparesis is a causative factor in delayed TTO [5] – motor fluctuations occur as a result of the delayed arrival of oral levodopa to the site of absorption in the small intestine [6, 7]. Various strategies to improve delayed ON and morning akinesia have been investigated including the use of dispersible or modified-release levodopa formulations or adjunctive therapies such as MAO inhibitors and long-acting dopamine agonists, such as rotigotine patch. However, while these approaches can decrease the severity of the morning akinesia OFF state, they do not result in a rapid or reliable TTO [8-11]. In his opinion, the best option is to select a non-oral therapy that bypasses the GI route, such as subcutaneous apomorphine injection.

This had been confirmed by interim results of the ongoing AM-IMPAKT (Apokyn for Motor IMProvement of Morning Akinesia Trial) which found that apomorphine injection significantly improved TTO in PD patients with morning akinesia, and was highly reliable with 95% of patients achieving at least a 20-minute reduction in TTO with an average reduction of 40 minutes (Figure 1) [12]. This improvement was also reflected in measures of QoL. Professor Isaacson highlighted the extensive clinical experience with apomorphine over the past 20 years which has shown it to be well tolerated, and the pen injection (Figure 2) is quick and easy for patients to use.

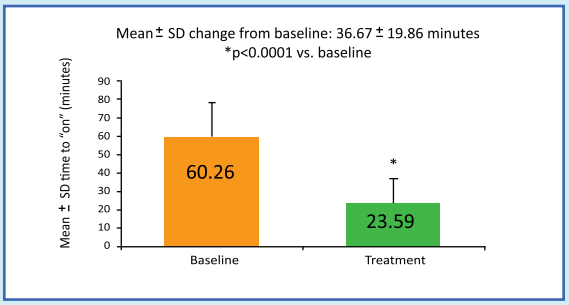

Figure 1: Interim results of the AM IMPAKT study. Change from baseline in daily time-to-ON shows a rapid response to apomorphine injection

Professor Claudia Trenkwalder (University of Goettingen, Paracelsus-Elena Klinik, Kassel, Germany) considerered that as morning akinesia reflected the nocturnal decline in levels of dopaminergic medication and insufficient night-time storage then the best strategy was to give appropriate medication at bedtime, such as a sustained-release dopamine agonist. Some patients might also require additional oral levodpa during the night and soluble levodopa on awakening.

Figure 2: Apomorphine pen injection

Professor Irena Rektorova (Department of Neurology, Masaryk University,Brno, Czech Republic) summed up the discussions and the pros and cons of these two alternative viewpoints, noting that apomorphine was the most potent of the available dopamine agonists having a rapid onset of action from as early as 7.5 minutes. She recognised however that each PD patient was different and that the selection of the most appropriate strategy to combat morning akinesia should be based on their individual symptoms and personal choice of treatment to suit their own circumstances.

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Prescribing information can be found on the adjacent page

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Introduction to the ACNR Stroke Series

The ischaemic penumbra is a concept familiar to all clinicians and scientists interested in ischaemic stroke. The concept of "potentially salvageable tissue" has revolutionised the practice of stroke medicine: intravenous thrombolysis is now routine, and other thrombus removal techniques are under active investigation. However, despite many years of investigation, how imaging the penumbra may help to select patients most likely to benefit from reperfusion treatment remains to be fully settled. In this article in our Stroke Series, we are very lucky to have a clear and authoritative account of the development of penumbral imaging - from initial experiments to recent randomised trials incorporating advanced MR imaging – by Josef Alawneh and Jean-Claude Baron. Standardisation of clinical application of penumbral imaging is clearly needed, and the limitations of simply applying the "pretty blobby maps" available commercially are made clear. However, recent randomised data give optimism that penumbral selection at various time windows in acute stroke will be useful in the future.

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Penumbral imaging in acute stroke: a triumph of hope over experience?

Summary

- Penumbra imaging for the selection of candidates for reperfusion therapy is widely used in routine clinical practice
- Randomised controlled trials using penumbra imaging, however, have been negative possibly due to inadequate methodology
- Further trials with improved design are ongoing

It's been more than thirty years since Astrup, Siesjö and Symon[1] described in a model of middle cerebral artery (MCA) occlusion in baboons the presence of two separate cerebral blood flow thresholds below which electrical and energy failure occur, respectively. They noted that between those two thresholds neuronal activity temporarily seizes but could potentially recover if perfusion is restored; this area resembled the half-shaded zone around the centre of a complete solar eclipse and thus was called 'the ischaemic penumbra'. The potential clinical benefits of its salvage and the importance of developing tools to identify it were already noted since those early days.

The first studies that proved the existence of the penumbra in acute stroke in humans used Positron Emission Tomography (PET) which has remained the gold standard imaging technique until now. Furlan et al[2] showed using ^{15}O-PET the presence of a critically hypoperfused tissue with high oxygen extraction fraction (OEF) that either recovered or progressed to infarction, whose volume correlated with acute neurological deficit and whose recovery was strongly associated with clinical improvement. Therefore, this tissue fulfilled all the prespecified operational criteria for the penumbra,[3,4] namely a) ischaemic brain tissue (CBF <20mls/100g.min, i.e., ~40% of normal, and high OEF), b) that is functionally affected, c) is of uncertain fate, becoming part of the infarct or recovering depending on subsequent (early) reperfusion, and d) whose survival, if any, underlies clinical recovery.[5]

The importance of treatments that can salvage the penumbra therefore became very apparent[6] and it wasn't long before salvage of penumbra was documented after IV thrombolysis using PET imaging.[7] However, PET imaging has several limitations precluding its widespread use in acute stroke; these include unavailability, technical difficulty and high cost. This in turn shifted the interest to other imaging modalities potentially able to depict the penumbra in the acute stage. One of these modalities is Magnetic Resonance Imaging (MRI) and in particular the development of the Diffusion Weighted and Perfusion Weighted Imaging (DWI and PWI respectively). The DWI sequence is very sensitive in detecting severely ischaemic tissue within minutes after stroke onset; furthermore, DWI lesions strongly predict final infarct within a few hours of an acute stroke and thus these lesions have been regarded as representing the infarct core. PWI, on the other hand, can depict all hypoperfused tissue and thus can identify not only the infarct core but also the tissue at-risk of infarction. It became, therefore, common to regard the mismatch between DWI and PWI as penumbral tissue due to its location outside the infarct core but still being at risk of infarction. Moreover, several early studies have shown that salvage of the DWI/PWI mismatch is associated with neurological improvement, thus fulfilling another of the cardinal operational criteria of penumbra.[9-11]

The DWI/PWI mismatch concept, however, has

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Jean-Claude Baron
trained in clinical neurology at the Salpêtrière Hospital, Paris, in Medical Physics at the CEA, Orsay, and in functional brain imaging at Harvard, USA. In 1986 he was appointed Inserm Director of Research, Director of the Inserm Unit and Scientific Director of the PET Centre in Caen, France. In 2000 he was appointed Professor of Stroke Medicine and Consultant Neurologist at Cambridge. Since 2010, he has been back at Inserm at the Centre for Psychiatry and Neuroscience, Sainte-Anne Hospital, Paris, and until recently still managed his Cambridge group as Emeritus Professor. He was awarded the Johannes Wepfer award of the European Stroke Conference in 2005.

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Table 1: Criteria defining patients with mismatch

STUDY	N	Time to treatment (hrs)	Perfusion lesion/core ratio	Perfusion lesion definition
DEFUSE	74	5.5	≥ 1.2 PWI/DWI	Tmax >2s
EPITHET	101	4.9 alteplase 4.85 placebo	>1.2 PWI/DWI	Tmax ≥ 2s
DIAS	104	5.4	≥ 1.2 PWI/DWI	MTT (without threshold)
DEDAS	37	7.4	≥ 1.2 PWI/DWI	Perfusion lesion not defined
DIAS II	186	6.5	≥ 1.2 (PWI/DWI, some with CTP)	Perfusion lesion not defined on CTP or PWI
Tenecteplase versus alteplase	75	2.7 alteplase 3.1 tenecteplase	≥ 1.2 CTP/Core	Transit time maps/core based on CBV (both without threshold)
DEFUSE II	99	4.5 (time to baseline MRI)	≥ 1.8 PWI/DWI	Tmax >6s
MR RESCUE	118	5.5 (time to enrolment)	≥ 1.4 PWI/DWI And CTP/Core	Tmax>6s

its limitations as well. One of these is that very early DWI lesions don't always represent the infarct core and can permanently reverse in part or in whole following acute reperfusion, thus behaving like penumbral tissue;[12] in addition, the precise penumbral perfusion thresholds on PWI imaging are still the matter of ongoing research. This has led researchers to search for other sequences that might depict the penumbra more precisely. One of these used the BOLD T2* MRI signal affected by deoxyhaemoglobin to map the OEF. This has been reported with varying success but hasn't been able to take over from the DWI/PWI paradigm so far.[13-15]

As an alternative to MRI, Computer Tomography Perfusion (CTP) imaging[16-18] has been extensively used to define the penumbra. Compared to MRI, it is more easily accessible and faster than MR; moreover, it is suitable for uncooperative patients and those with possible MR contraindications. Recently the methodology using CTP has improved to provide both full brain coverage and CT angiogram following a single contrast injection. CTP thresholds to identify core and penumbra have been validated by comparing to the final infarct[19-23] and by clinical correlations.[19, 22, 24, 25] However, the uncertainties of the still imprecise penumbral thresholds that exist with PWI apply to CTP as well; with in addition the issue of poor signal to noise ratio in severely hypoperfused areas.

Clinical trials

Despite the extensive research on imaging penumbral tissue, the first positive randomised controlled studies (RCTs) on IV thrombolysis in acute stroke used straightforward non contrast CT head to exclude haemorrhage and no penumbral imaging.[26,27] This was a pragmatic and immediately widely applicable approach, but it deprived us from assessing whether selecting patients for thrombolysis using penumbral imaging is of benefit in the first 4.5 hours after stroke onset. However, several open-label cohort studies using DWI/PWI mismatch to select patients for thrombolysis beyond the proven time window were promising[28-31] and opened the way for large-scale prospective studies applying the mismatch concept. One of those studies was DEFUSE,[32] a prospective open-label study aiming to determine whether baseline MRI profiles can identify patients who would benefit from reperfusion between 3-6 hours post onset. However, the hypothesis of the study was reviewed in an interim analysis; a subgroup of patients who had unfavourable outcome was identified and labelled as the 'malignant profile'; those patients were excluded and the remaining patients with mismatch were labelled as the 'target mismatch' profile. Target mismatch was defined as PWI/DWI ratio ≥1.2, with PWI lesion defined as Tmax >2s and ≥10ml (Table 1), and the 'malignant profile' as the presence of a DWI lesion and/or severe (Tmax≥8s) PWI lesion ≥100mls. The study showed that reperfusion in patients with the 'target mismatch' profile was associated with favourable outcome when compared to reperfusion in patients with no mismatch.[32,33]

The first randomised placebo controlled study that prospectively acquired MRI with DWI/PWI imaging before iv thrombolysis was the EPITHET study, which aimed to test the validity of the mismatch concept in the 3-6 hours time window.[34] However, the study design was to assess in retrospect whether the presence of mismatch was a predictor of good response to iv therapy versus placebo, i.e., randomisation was not based on MRI criteria. Patients with mismatch were defined as those with PWI/DWI ratio >1.2 and a PWI-DWI volume ≥10ml, with the PWI lesion defined as tissue with Tmax ≥2s (Table 1). 101 patients were randomly assigned to receive alteplase or placebo. The primary endpoint was infarct growth between baseline DWI and day 90 T2 lesion in the mismatch patients only, and this was non-significantly lower in the alteplase group. The study found, however, that alteplase was significantly associated with reperfusion in the mismatch group, and reperfusion in turn was significantly associated with better neurological outcome. However, as will be discussed below, post-hoc reanalysis of this dataset using more appropriate perfusion thresholds and endpoints showed strongly positive results. The need for larger randomised studies using well-designed penumbra imaging in the inclusion criteria became ever more apparent following this study.

Around the same time two pilot studies (DIAS and DEDAS) of a new thrombolysis drug were published. DIAS was a dose-finding phase II randomised trial designed to evaluate the safety and efficacy or intravenous desmoteplase, a novel plasminogen activator, administered within 3-9 hours of ischaemic stroke onset in patients with perfusion/diffusion mismatch on MRI (Table 1).[35] Part 1 of the trial was terminated prematurely due to the high rate of symptomatic intracranial haemorrhage (sICH). Following reduction in the administered dose, part 2 of the study showed lower rates of sICH using doses up to 125µg/kg. The conclusions were that desmoteplase in patients with mismatch was associated with a higher rate of reperfusion rates and better clinical outcome compared with placebo. This pilot study was followed by DEDAS[36] which also used perfusion /diffusion mismatch ratio ≥1.2 to assess the safety and efficacy of desmoteplase 90µg/kg and 125µg/kg in patients with acute ischaemic stroke 3-9 hours after onset. This small phase II study (n=37) confirmed the findings of DIAS that IV desmoteplase at those doses is safe and may improve clinical outcome.

The findings of the above two phase II desmoteplase studies led to the first large phase III study that used penumbra imaging in its inclusion criteria. DIAS II[37] was a randomised, placebo-controlled, double blinded, dose-ranging study comparing desmoteplase 90 µg/kg and 125 µg/kg versus placebo in acute ischaemic stroke given 3-9 hours after onset. The primary end point was clinical response rate at day 90, defined as a composite of improvement in NIHSS score of ≥ 8 points or an NIHSS score ≤ 1, a modified Rankin scale score 0-2, and a Barthel index of 75-100. 193 patients were randomised, and 186 patients received treatment: 57 received 90µg/kg desmoteplase; 66 received 125µg/kg desmoteplase; and 63 received placebo. The clinical response rates at day 90 were 47% for 90µg/kg desmoteplase, 36% for 125µg/kg desmoteplase and 46% for placebo, showing no statistical benefit of desmoteplase given 3-9 hours after onset of stroke. Patients were included if they had a distinct 'penumbra' with a perfusion lesion/core ratio ≥1.2 based on MRI (PWI/DWI) or CT (CTP/CT) (Table 1).

Although the desmoteplase trials deliberately applied still unproven imaging markers to a time-window beyond those investigated in observational studies, a strategy that in retrospect was unlikely to meet with success, the negative results of DIAS II came as a surprise to the stroke community at large, and raised several questions on the imaging definition of penumbra as will be discussed below.

To enrich the population studied by recruiting a more homogeneous group, a randomised trial of tenecteplase versus alteplase for acute ischaemic stroke used the presence of penumbra on perfusion imaging as an inclusion criterion, in order to enrich the population studied by recruiting a more homogeneous group.[38] This novel design allowed them a considerable reduction of the required sample size. This was a Phase 2B 3-arms trial that assigned 75 patients to receive alteplase (0.9mg/kg) or tenecteplase (0.1mg/kg or 0.25mg/kg) less than six hours after stroke onset. Inclusion criteria included the presence of perfusion lesion at least 20% greater than core, with volume of at least 20 ml and an associated vessel occlusion on CTA. Perfusion lesions were based on CTP transit-time maps, and core defined using cerebral blood volume maps. The coprimary end points were the proportion of the perfusion lesion that was reperfused at 24 hours on MRI PWI and the extent of clinical improvement at 24 hours assessed on the NIHSS score. Together, the two tenecteplase groups had greater reperfusion (p=0.004) and clinical improvement (p<0.001) at 24 hours than the alteplase group with no significant differences in serious adverse events. In this study, time to treatment was 2.7 hours in the alteplase group and 3.1 hours in the tenecteplase group which is the earliest that a randomised study with penumbral imaging had achieved. However, there was no control arm in this study (which would have been unethical to have) and so no comparison is available to a control group that was not treated.

The above studies were exploring IV thrombolysis treatment; and while one would expect similar findings with endovascular reperfusion, the time came for that to be proven. DEFUSE 2[39] was set up to address the question: Can MRI identify patients who are most likely to benefit from endovascular reperfusion? This was a prospective study that enrolled consecutive patients scheduled to have endovascular treatment within 12 hours of onset of hemispheric stroke. Patients had acute MRI imaging at baseline before treatment to assess the presence of 'target mismatch' and had repeat MRI within 12 hours to assess for reperfusion and a later structural MRI to assess final infarct. The primary outcome was favourable clinical response, defined as an improvement of 8 points or more on the NIHSS between baseline and day 30 or a score of 0-1 at day 30. Ninety-nine patients were included in the analysis; 78 patients had target mismatch and 59% of them had reperfusion; 21 had no target mismatch and 57% of them had reperfusion. The adjusted odds ratio for favourable clinical response associated with reperfusion was 8.8 in the target mismatch group and 0.2 in the no target mismatch group (p=0.003). Interestingly, the clinical benefit from reperfusion was not significantly different between patients in the ≤6 hours and those in the 6-12 hours time window, suggesting that penumbral imaging is able to identify patients who would benefit from late intra-arterial therapy even beyond 6 hours and up to 12 hours, after clinical onset. It is important to note that the perfusion parameters to define target mismatch in this study had been modified from DEFUSE and made more specific for the penumbra as follows: Tmax >6s and mismatch ratio ≥1.8 (Table 1); furthermore, mismatch volume had to be ≥15ml, DWI lesion <70ml and severe (Tmax>10s) perfusion lesion <100ml. Around half of the patients received IV rt-PA before endovascular procedure and the median onset from stroke onset to baseline MRI was 4.5 hours.

The need for a randomised study of endovascular treatment using penumbra imaging was apparent and MR RESCUE 40 was designed to address that. One hundred and eighteen patients were randomly assigned within 8 hours after the onset of large-vessel anterior circulation stroke to undergo mechanical embolectomy or receive standard care. Patients underwent pretreatment computer tomography or magnetic resonance imaging of the brain and randomisation was stratified according to whether the patient had a favourable penumbral pattern (substantial salvageable tissue and small infarct core) or non-penumbral pattern (large core or small/absent penumbra). Favourable penumbral pattern was assigned on a CT or MRI brain if the predicted infarct core was ≤ 90ml and when the proportion of predicted infarct tissue within the at-risk region was ≤ 70% (i,e mismatch ratio around 1.4; table 1)[41]. The primary outcome was the 90 day mRS mean score. The mean age was 65.5 and the mean time to enrolment was 5.5 hours; 58% had a favourable penumbra pattern. Mean scores on the mRS did not differ between embolectomy and standard care (3.9 vs 3.9, P=0.99). Embolectomy was not superior to standard care in patients with either a favourable penumbral pattern (mean score 3.9 vs 3.4, P=0.23) or non-penumbral pattern (4.0 vs 4.4; P=0.32). As a conclusion the authors stated that a favourable penumbral pattern on neuroimaging did not identify patients who would differentially benefit from endovascular therapy for acute ischaemic stroke nor was embolectomy superior to standard care. However, as will be discussed below, this study has been criticised and its results called into question.

Discussion

We reviewed above the major thrombolysis or acute interventional studies that included penumbral imaging in their inclusion criteria. A first observation is that while the results of the pilot and observational studies were promising, those of the main randomised studies were negative. This raised important questions regarding the methodology used, and even some went as far as questioning the penumbral concept itself. The possible reasons for these negative results will be explored here by attempting to answer the question: Why did EPITHET, DIAS II and MR RESCUE fail to support the notion that using penumbral imaging is clinically useful?

To start with, as already noted, when the first positive alteplase study[26] was conducted, imaging of the penumbra was not widely available and thus wasn't required for recruitment. Subsequently, once alteplase was licensed for use within 3 hours of stroke onset, the emphasis was to get plain CT imaging swiftly and very little room was left for any research on penumbra imaging within that 3 hour window. The first thrombolysis studies using penumbral imaging (EPITHET and DIAS II), therefore, recruited patients beyond the 3 hours, looking into extending that window. This deprived us, however, and perhaps for ever, of any evidence of the clinical benefit from penumbra imaging in the first 3 hours post stroke onset, at a time when penumbral tissue is expected to be the largest. This was despite the suggestion from observational studies that penumbral imaging even within the 3-hour window enhanced the clinical benefit from iv t-PA.[29] The challenge faced by EPITHET and DIAS II, therefore, was to capture this shrinking penumbra beyond 3 hours and prove that its salvage was of clinical benefit. While this has proved to be very hard, the negative results from the primary analysis of those two studies have provided us with important lessons for the future.

One of the cardinal questions these two studies had to address was how to define penumbral tissue using MR; and both EPITHET and DIAS II relied on the PWI/DWI mismatch concept. EPITHET used Tmax ≥2s as the perfusion threshold to define penumbral tissue and DWI lesion for the core; DIAS II used any perfusion abnormality seen without specifying a threshold as the penumbral threshold and the DWI lesion again as the core. In retrospect, it is now clear that these definitions were too liberal and resulted in the inclusion of significant oligaemic tissue that was not dysfunctional nor at risk.[42] Observational studies that directly compared MRI perfusion parameters to PET reported Tmax values around 5.5s as the closest to the penumbral threshold;[43-45] implying that significant amounts of the tissue regarded as penumbra in those studies were mere oligaemia. In DIAS II the perfusion/core mismatch ratio in percentage was reported to be >500% more than 6 hours after stroke onset; this, indeed, is unlikely to represent true penumbral tissue at those late time points. Moreover, up to 67% of patients screened were thought to have significant mismatch volume

at 6 hours post onset, again a very large proportion which might have included patients with oligaemia but not true mismatch. To address the above, a post hoc analysis was recently published that refined the definition of mismatch, first in DIAS II, and then in a pooled cohort from DIAS, DEDAS and DIAS II.[46] Mismatch was re-defined as the difference between the calculated volume of hypoperfusion based on MTT maps (no defined threshold) and volume of DWI, but tested only in patients with mismatch volume >60ml. The difference in favourable response rate to desmoteplase between placebo and treatment group increased with the new definition but was statistically significant only in the pooled analysis. The authors concluded that desmoteplase appears beneficial in patients with large mismatch volume but that this will need to be tested in prospective studies. Along the same lines, in EPITHET significant oligaemic tissue was regarded as penumbra and it is suspected that a sizeable number of patients were misclassified. This is supported by the fact that the vast majority of patients (86%) screened were judged to have significant mismatch volume 3-6 hours post onset, again a clear overestimation. And when penumbra was redefined in a post hoc analysis using a threshold of Tmax>6s and proper image co-registration, the median mismatch volume fell from 126ml to 37ml and only 53% of patients were now found to have had true penumbra. This lead to several patients being reclassified, and a reanalysis with the new definition of penumbra including pooled patients from DEFUSE showed that favourable tissue and clinical outcome from reperfusion in the target mismatch group became statistically significant.[33]

The other important question the above two studies had to address was what mismatch ratio is to be considered significant. This is the ratio of total affected tissue divided by core. Increasing the ratio would decrease the absolute volume of mismatch and also the chances of observing clinical improvement should that mismatch tissue survive; however, the more you increase the ratio, the more patients will be excluded as having no mismatch. Both DIAS II and EPITHET used 1.2 as their cut-off ratio, meaning that the affected but not core tissue 'penumbra' had to be at least 20% larger than the DWI lesion 'core', which in retrospect seems small. As the results of both trials were negative, subsequent studies used larger ratios in order to maximise the chances of capturing and saving clinically relevant mismatch. MR RESCUE used a ratio around 1.4 but failed to demonstrate any positive effect. DEFUSE II went up to 1.8 and had more promising results; however, this was an observational study with no randomised control arm. In order to address the question of which should be the optimum ratio to use, a reanalysis of the DEFUSE data was carried out, which evaluated the odds ratio for a favourable clinical response in mismatch patients with reperfusion compared with no reperfusion for various mismatch ratio thresholds.[47] A mismatch ratio of 2.6 provided the highest sensitivity and specificity for identifying patients in whom reperfusion was associated with favourable response. Such a high mismatch ratio has not been tested in any randomised study yet, but clearly would considerably reduce the number of recruitable patients.

Indeed, an important aspect of these studies is the number needed to recruit to be able to show significant difference in clinical response. The aim of penumbra imaging is to screen patients and select those who are most likely to benefit from thrombolysis and thus reduce the total number of participants in the studies. However, this hasn't happened on the ground as shown above; and thus larger numbers of patients possibly were eventually needed to demonstrate any benefit as the screening process has not been optimum. For example the NINDS study,[26] the first to demonstrate benefit from rtPA within the first 3 hours recruited 333 patients at a time-point where penumbra is expected to be large. ECASS III had to recruit 821 patients to demonstrate thrombolysis benefit between 3 and 4.5 hours post onset.[27] EPITHET recruited only 101 and DIAS II 186 patients. While these numbers are relatively large compared to previous imaging studies, they are quite small compared to previous thrombolysis studies; particularly if you take into account that recruitment was between 3-6 hours at a time where penumbra volume has significantly declined. On the other hand, the above-mentioned tenecteplase trial requiring presence of penumbra as an inclusion criterion needed only 25 patients per arm to document efficacy. Calculating the sample size needed for those trials is challenging due to difficulty in estimating an accurate treatment effect. It is been estimated that about 330 patients will be needed in a study using penumbral imaging before thrombolysis treatment.[48]

We addressed above the difficulties related to penumbra imaging in the two large IV thrombolysis studies. It is also expected that trials using an endovascular approach would face the same issues. This was noted in the MR RESCUE[40] trial which used penumbra imaging before intervention. Here Tmax >6s threshold was used to define mismatch; mismatch ratio of around 1.4 was used which is marginally but definitely better than the 1.2 previously used; and the mean time to enrolment was 5.5 hours. The total number of patients recruited was 118 but those with a favourable penumbra pattern were only 68 (34 embolectomy and 34 standard care group) thus significantly reducing the power of this study. An additional confounder in this study was that a percentage of the patients had IV thrombolysis before enrolment. This may be relevant to the fact that despite allocation to embolectomy, recanalisation and reperfusion rates were similar between the treatment and control group. Reperfusion is the most important factor leading to salvage of the penumbra, and without it, no matter the volume of penumbra, good recovery is unlikely. Taking all the above limiting factors together, plus the fact that this study started many years ago and therefore used largely outdated thrombectomy devices and that both MR and CT perfusion were used to determine the favourable penumbral pattern, maybe it is not surprising that it was negative.

...although already widely used in clinical routine, penumbra imaging for the selection of candidates for reperfusion therapy both within and beyond the current licensed time-window for iv thrombolysis has not been validated yet

There are a few additional difficulties that studies aiming at imaging the penumbra have to face. One is the post-processing used after acquiring the imaging. Various methods can be used, leading to different maps, each providing potentially different information.[48,49] There has been no consensus yet on the best methodology, software, maps and thresholds to use for each particular method; however, there are recommendations regularly published addressing these topics (Stroke imaging research roadmap)[50] which would be advisable to adhere to in order to improve consistency between studies. This remains a topic of active research and there is still some way to go until these questions are resolved. However, proprietary issues are involved here as well, as, at the moment each manufacturer offers commercial software which works as a 'black box' that delivers pretty blobby maps of penumbra and core of unclear physiological validity. In addition, in order for post-processing tools to be useable in clinical trials and also in future routine practice, they must consistently deliver reliable core/penumbra maps within a minute or two of data acquisition at most. Recently developed tools are being tested currently.[33]

While the future of penumbra imaging in acute stroke within or beyond treatment

window is uncertain, there are several potential uses of penumbral imaging which would be useful to explore in future studies. Within the 4.5 hours window, future imaging-based studies could address the following issues: a) exclusion of patients who would not benefit from treatment such as those with no perfusion deficit or already extensive core; b) exclusion of patients who might be harmed by treatment (i.e high bleeding risk); c) inclusion of patients who might benefit but are otherwise often excluded like those with mild, improving or fluctuating deficits; and d) exploring additional treatment options in those who have not rapidly recanalised after initial thrombolysis, such as 'bridging' from iv to intra-arterial therapy. Outside the 4.5 hour window, future studies could explore the following: a) inclusion of selected patients with significant mismatch and small core after taking in to consideration the issues addressed in this review; and b) inclusion of patients with unknown time of onset (e.g., awakening stroke). A few ongoing studies are currently attempting to address some of the above questions. One of them is EXTEND, which is exploring IV thrombolysis beyond thrombolysis window in selected patients based on penumbral imaging (ClinicalTrials.gov Identifier: NCT00887328; accessed 24/08/2013). This trial recruits patients between 3-9 hours post stroke onset. Penumbral imaging inclusion criteria include: a mismatch ratio >1.2, a DWI volume ≤70mL and a PWI-DWI difference >10 ml. Perfusion lesion is defined as tissue with Tmax > 6 second. While the perfusion threshold chosen here is appropriate to identify the penumbra, the mismatch threshold used is similar to previous negative studies. Another, similarly designed trial to be run in Europe is ECASS 4, currently being set up. A third study, from China, entitled "Imaging-based Thrombolysis trial in Acute Ischemic Stroke-II (ITAIS-II)"[51] also recruits patients 3-9 hours post stroke onset; this study is using CT perfusion in the inclusion criteria and eligible patients are those with significant perfusion deficit defined by a perfusion lesion >2cm diameter.

This study also opted for a mismatch ratio of 1.2 and requires the presence of large vessel occlusion on CTA as well. It will be interesting to see the results of this study that uses a completely new method of defining patients with significant perfusion deficit.

We have reviewed above how the ischaemic penumbra has evolved over the last three decades from a mere thought to a lab experiment, then to a proven concept, and nowadays it is a daily topic in almost every research or clinical stroke meeting. However, despite the intensive research done so far, and the extensive use of penumbral imaging worldwide,[48] the evidence supporting its use in the treatment of acute stroke has significantly lagged behind.[52] We explored the potential reasons for this situation and provided some guidance for future research taking into account the lessons learned. It is nevertheless a fact of life that acute stroke MR- or CT-based protocols including perfusion imaging on top of DWI, MR angiography and Gradient Echo for the former, and plain CT and CT angiography for the latter, are increasingly used worldwide in daily routine, not just beyond the licensed time-window for iv t-PA but also within it. This is supported by numerous scientific articles pointing to the overall clinical benefits from the array of diagnostic, aetiologic and pathophysiological information provided even beyond penumbra imaging, and used to guide overall patient management - although not based on definitive scientific evidence as yet.

Conclusions

The concept and the presence of penumbra have been documented by extensive experimental and clinical investigations over the last few decades. However, although already widely used in clinical routine, penumbra imaging for the selection of candidates for reperfusion therapy both within and beyond the current licensed time-window for iv thrombolysis has not been validated yet, perhaps due to inadequate methodology, and randomised controlled trials with improved design are ongoing. ◆

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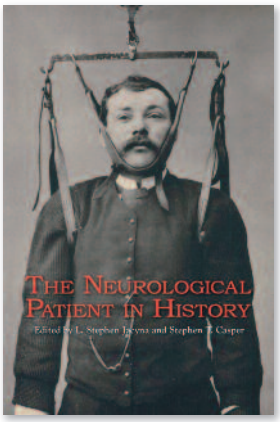
The Neurological Patient in History



Editors: Jacyna LS, Casper ST
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Reviewed by:
AJ Larner, Cognitive Function Clinic, WCNN, Liverpool.

The history of neurology has traditionally been told by neurologists about neurologists … for neurologists. This includes their biographies, and their accounts of research, institutions, and treatments, in what may be termed a "top down" approach.

By contrast, the voice of the neurological patient has been largely neglected. This is paradoxical in the sense that the neurological encounter is (ideally) dominated by hearing the patient's account. It is predictable in the sense that written patient narratives rarely enter the historical record. Such a "bottom up" approach to medical history was advocated most cogently by Roy Porter (1946-2002) some 30 years ago. His plea may have ultimately led to the current volume, examining the neurological patient in history. The editors are well-known historians: Stephen Jacyna co-authored with Edwin Clark the seminal *Nineteenth-century origins of neuroscientific concepts* (Berkeley: University of California Press, 1987) and has written a biography of Henry Head. Stephen Casper wrote his PhD on British Neurology and has spoken on historical topics at ABN meetings.

The book is divided into several sections which examine the various ways in which the neurological patient is constructed. The construct, it is argued, derives from medical practice, patient 'groups', historians, and, of course, individual patients. The latter section is the only one in which the authentic voice of the patient is heard. For example, we hear of the "psychasthenia" of Poet Robert Nichols, sometime patient of Henry Head, through his letters to the neurologist after his retirement. However, even in this section, the voice is sometimes mediated by others, e.g. Gwen Raverat's letters about her husband Jacques' experience of multiple sclerosis. Ballenger documents the evolution of ideas about dementia, from its representation as the entire loss of selfhood through to the assertion of selfhood by "famous" AD patients such as Ronald Reagan. Howard Kushner gives a fascinating account of views on Tourette's syndrome, in particular its psychoanalytic representations, which sometimes directly contradicted patient reports. Casper's chapter on the evolution of the neurological examination is probably the most pertinent for practitioners of the art of Clinical Neurology.

This is a book for medical historians by medical historians (to my knowledge Kushner is the only medically qualified contributor). This has led to some pretty semantically dense material, which may not be quite the most suitable reading matter for the interstices of the outpatient clinic! There is an attempt at clarification on page 215: "Each of these chapters is a register of the historically constituted episteme of its author". This was my favourite, and I still have absolutely no idea what it means!

Moreover, there are some astonishing errors for which authors and editors must take responsibility. Two of the giants of neurology are ascribed incorrect middle initials (William Gowers given an A instead of an R, p 41; William Lennox given a J instead of a G, pp 52,55). One of the most famous of all neurological patients, the amnesic HM, is said to have lived to 2009 (p223), but in fact died in 2008.

Nevertheless, the book demonstrates that the neurological patient is a cultural construct, dependent on the context in time and place, which ought to be of interest to the neurological practitioner.

Cerebral venous sinus thrombosis caused by paroxysmal nocturnal haemoglobinuria: a rare cause not to be missed

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Paroxysmal Nocturnal Haemoglobinuria, Cerebral Venous Sinus Thrombosis, Headaches, Confusion, Stroke.

Summary
We present a case of cerebral venous sinus thrombosis (CVT) caused by paroxysmal nocturnal haemoglobinuria (PNH). Although a rare cause of a rare condition, PNH can be diagnosed with a single blood test and has a poor prognosis if untreated. However therapy with the anti-complement drug, eculizumab, is very effective treatment. Eculizumab usually prevents further thrombotic problems, meaning that early diagnosis is critical. Our approach to investigating the cause of CVT has changed as a result of this case and we believe that PNH is a condition that neurologists dealing with CVT should be aware of.

Case report

An elderly patient experienced a sudden onset of visual problems characterised by an inability to send a text message on their mobile phone, set the burglar alarm at their house or read the newspaper. The episode was associated with a mild, throbbing, bi-temporal headache that reached maximum intensity over a couple of minutes. The headache lasted for 30 minutes before resolving spontaneously but vision did not improve. The patient arranged to visit the opticians a few days later. Bilateral papilloedema was identified and she was urgently referred into hospital.

Past medical history included a portal vein thrombosis diagnosed in 2006 which lead to the development of non-cirrhotic portal hypertension. In 2008 the patient became anaemic without an underlying cause identified. At the same time they had an episode of haematemesis secondary to oesophageal varices caused by portal hypertension. To help reduce portal venous pressures the patient underwent a transjugular intrahepatic portal-systemic shunt (TIPSS) insertion and remained under hepatology follow up. The patient developed further thromboses within the TIPSS in 2010 and underwent a TIPSS thrombectomy and further stent insertion. In 2011 recanalisation was attempted via clot retrieval and thrombolytic therapy. This thrombolysis treatment was successful but the TIPSS clotted again in March of 2012. Other medical history included poliomyelitis as a child.

Examination in hospital revealed bilateral reduced visual acuity to 6/12 with normal visual fields to confrontation and normal pupillary reactions. Inspection of the fundi confirmed bilateral grade 4 papilloedema. The remainder of the neurological examination did not demonstrate any new focal neurology and general physical examination was normal.

An MRI brain scan and MR venogram showed an acute posterolateral frontal lobe infarction and demonstrated filling defects in the mid and posterior aspect of the superior sagittal sinus (Figure 1). A diagnosis of venous cortical infarct and venous sinus thrombosis was made. Thrombophilia screen testing for antithrombin III, protein C, activated protein C resistance, protein S, lupus anticoagulant, prothrombin gene mutation, factor V Leiden mutation and anticardiolipin antibodies were normal.

Treatment was commenced with low molecular weight heparin and then converted to oral anticoagulation with warfarin. The patient's visual acuity did not improve and remained at 6/12 bilaterally. A further admission to hospital occurred one month after discharge, because the headache returned, but no new abnormality was identified on repeat imaging. During that admission, results of a test for PNH that had been performed by the hepatologists at an out-patient clinic appointment the previous week demonstrated 93.33% of the patient's cells were PNH. The patient was urgently reviewed by the haematologists and commenced treatment with eculizumab, a monoclonal antibody that inhibits the formation of terminal complement.

Discussion

Cerebral venous sinus thrombosis is an uncommon condition thought to affect approximately five people per million annually.[1] Although there are over 100 different aetiologies for CVT, in 12.5-20% of cases an underlying explanation cannot be found.[2,3] CVT causes can be divided into acquired risks (such as cancer, pregnancy, oral contraceptive use) and genetic risks (such as the inherited thrombophilias).[4] The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), the largest prospective observational study, included 624 adult cases of CVT and found that thrombophilia was the most common risk factor, seen in 34% of patients.[5]

PNH is an extremely rare condition with an incidence of around 1.3 per million of the population.[6] It is caused by somatic mutations of the PIG-A gene, one of a number of genes needed for the synthesis of the glycophosphatidylinositol (GPI) anchor. The GPI anchor is made in the endoplasmic reticulum and then transported to the surface of the blood cell where it is needed by a variety of cell surface proteins for them to be expressed.[7] Lack of function of the GPI protein leads to the absence or reduced expression of key cell surface molecules on blood cells. This renders the cells susceptible to complement mediated attack which causes intravascular haemolysis and platelet activation. This intravascular haemolysis is the hallmark of the disease and as well as being

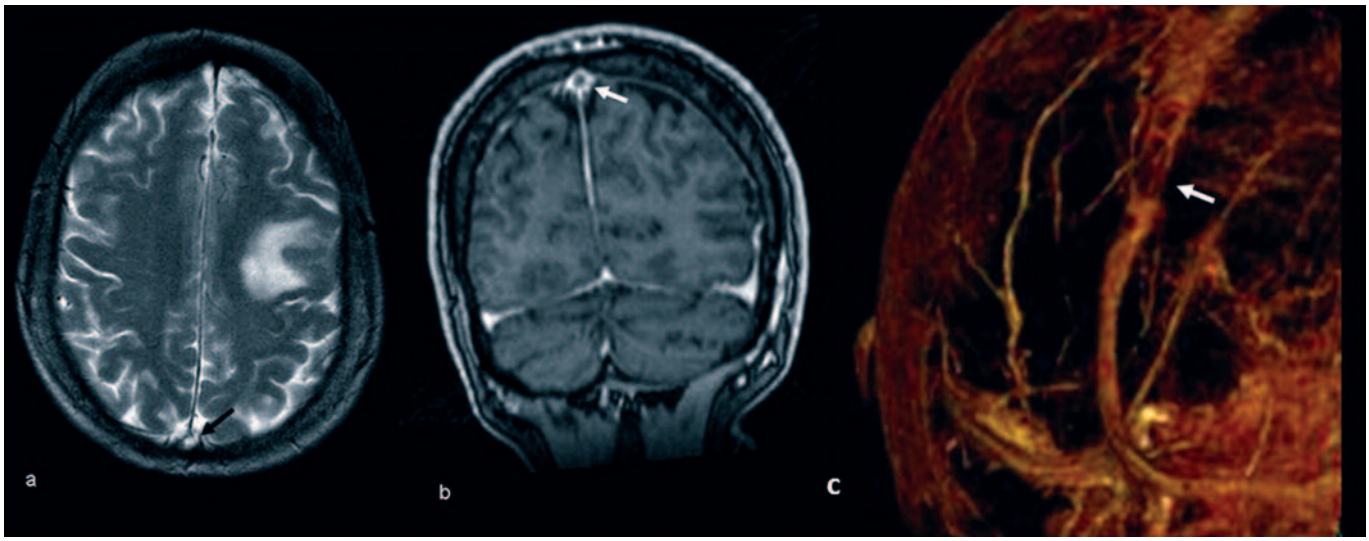

Figure 1: Image A shows the ischaemia associated with the venous sinus thrombosis and the thrombosis in the posterior aspect of the superior sagittal sinus (Black Arrow). Both images B and C show the filling defect (White Arrows) caused by the thrombosis.

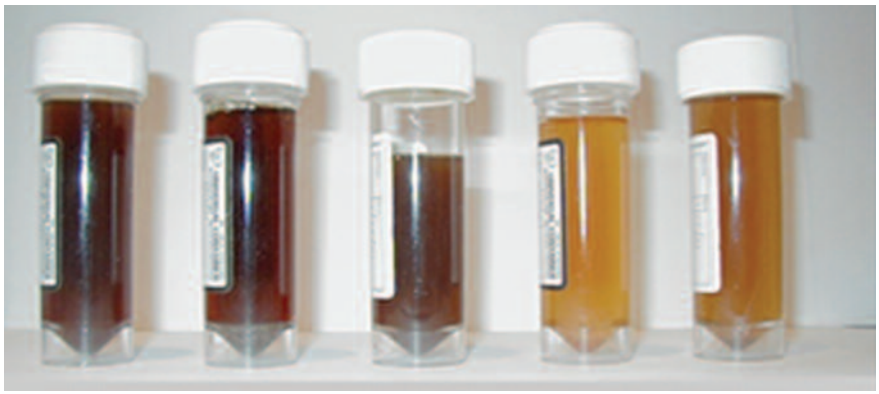

Figure 2: The urine of a PNH patient can change colour throughout the day. Haemoglobinuria is usually most marked in the morning. All the above samples were produced by a single patient in one day.

anaemic, patients can experience symptoms including haemoglobinuria, dysphagia, recurrent abdominal pain, dyspnoea, severe lethargy and renal impairment. Classically haemoglobinuria is worse in the morning. Urine colour can change dramatically throughout the day (Figure 2). However, not all patients with PNH describe this symptom so the disease should still be suspected.

PNH causes an increase in mortality as well as morbidity. A study on a British population revealed that patients with PNH, with an average age at presentation of 42 years, treated with supportive measures only had a median survival of only 10 years.[8] The main cause of death in PNH is thrombosis with up to 39% of patients developing thromboemboli at some point.[8] Once an individual develops a thrombosis their risk of dying is increased by between 5 to 15 times.[8,9] Anticoagulation once a thrombosis has occurred is often ineffective. Thromboses in people with PNH, which may be arterial as well as venous, often develop in unusual sites, such as cerebral, mesenteric, hepatic and portal veins.[10]

Testing for PNH involves sending a blood sample for flow cytometry.[7,11] Flow cytometry for the GPI-linked proteins is available through most laboratories around the UK. Once a diagnosis is made patients should be referred to one of the two nationally commissioned PNH centres. These are based in St James's University Hospital in Leeds or Kings College Hospital in London.

Treatment of PNH was predominantly supportive until the monoclonal antibody, eculizumab, was licensed in 2007. Eculizumab binds to the complement protein C5, arresting the complement cascade and therefore preventing terminal complement activation and haemolysis of red cells.[7] Clinical trials have shown that eculizumab dramatically decreases the risk of venous-thromboembolism.[10] Although not a cure, patients with PNH who are treated with eculizumab have survival rates comparable with age and sex-matched normal controls.[12] Blocking the cleavage of the C5 protein increases the risk of developing infections with *Neisseria Meningitidis* and so vaccination is required prior to starting treatment.[7]

International experts in PNH suggest this disease should be tested for in all cases of CVT.[11] We now test for PNH in cases of unexplained CVT, in cases where there is a past history of venous thrombosis and where there is evidence of anaemia, other cytopenia or intravascular haemolysis.

PNH is a rare but important condition that neurologists should consider when managing patients with CVT. Thrombosis in the setting of PNH is an urgent indication to commence eculizumab through the National PNH Service. Before this case PNH did not enter our differential diagnosis. The poor outcomes seen in untreated PNH, and the significant improvements once treated with eculizumab, makes it a diagnosis not to be missed. ◆

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Introduction to the Regeneration Series

In this issue of ACNR we start a new series on regenerative therapies. We hope to capture some of the new developments in this fast expanding field, a field that includes the prospect of stem cell based therapies in the treatment of a range of neurodegenerative disorders. In this first article we have a fabulous overview of cell therapies for Parkinson's disease from the team in Lund, Sweden, where the pioneering work developing this whole approach started over 30 years ago.

Roger Barker, Series Editor.

Cell therapies for Parkinson's disease

Summary

- Grafted fetal dopaminergic cells can provide long-lasting benefit in PD patients
- For large-scale application, human embryonic stem cells, induced pluripotent cells and induced neurons are currently being developed
- Unique medical risks and ethical issues are connected with these new cell sources

Parkinson's disease – focal dopaminergic cell loss

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting an estimated 10 million people worldwide and approximately 100,000 people in the UK.[1] Progressive loss of mainly (but not only) dopaminergic neurons, located in the substantia nigra and projecting to the striatum, leads to a striatal dopamine deficit, resulting in cardinal motor symptoms such as rigidity, bradykinesia and tremor. This relatively focal neuronal degeneration makes PD a good candidate for cell replacement therapies.

Proof-of-principle from foetal midbrain transplants

Studies in animal models of PD using foetal DA neurons, have shown that neuronal replacement and partial reconstruction of damaged neuronal circuits is possible. This work formed the basis for pioneering foetal cell transplantation trials in PD patients in 1987 in Lund, Sweden.[2] Since then, many more trials have taken place worldwide with patients receiving foetal cell grafts. Trials were initially performed in a small group of patients using open-label study designs, and results were variable, spanning from no effect to impressive and long-lasting clinical benefit.[3] Generally, in the open labelled trials approximately two thirds of the patients showed substantial improvement, whereas one third did not (for review see reference [3]). Mean improvement in the United Parkinson's disease rating sale (UPDRS, shown in % with 95% CI)) ranged from -43% (-65.02-21.38, n=12),[3,4] 37.79% (-49.95 to -25.64, n=14)[3,5] to -11.47 (-21.83 to -1.12, n=10).[3,6,7] Even though results were variable, the trials provided important proof-of-concept that a long-lasting and sustained clinical improvement is achievable with foetal cell transplantation. The clinical improvement was paralleled by an unbiased increase in dopamine transporter (DAT)-binding, a marker for striatal dopaminergic fibres. The increases have been shown to persist for up to 18 years after grafting, and

in some cases have made pharmacological medication almost unnecessary.[8] However, two NIH-sponsored, double-blind, placebo-controlled clinical trials performed in the USA failed to show clinical benefit.[9,10] These studies also reported that a considerable proportion of patients (15%, 5/33[10] and 57% 13/23[9]) developed dyskinesias even in the OFF state (without medication). However, when these studies were further analysed, patients < 60 years[10] or with less severe disease at baseline, did show a significant improvement,[9] with similar observations in PET imaging results.

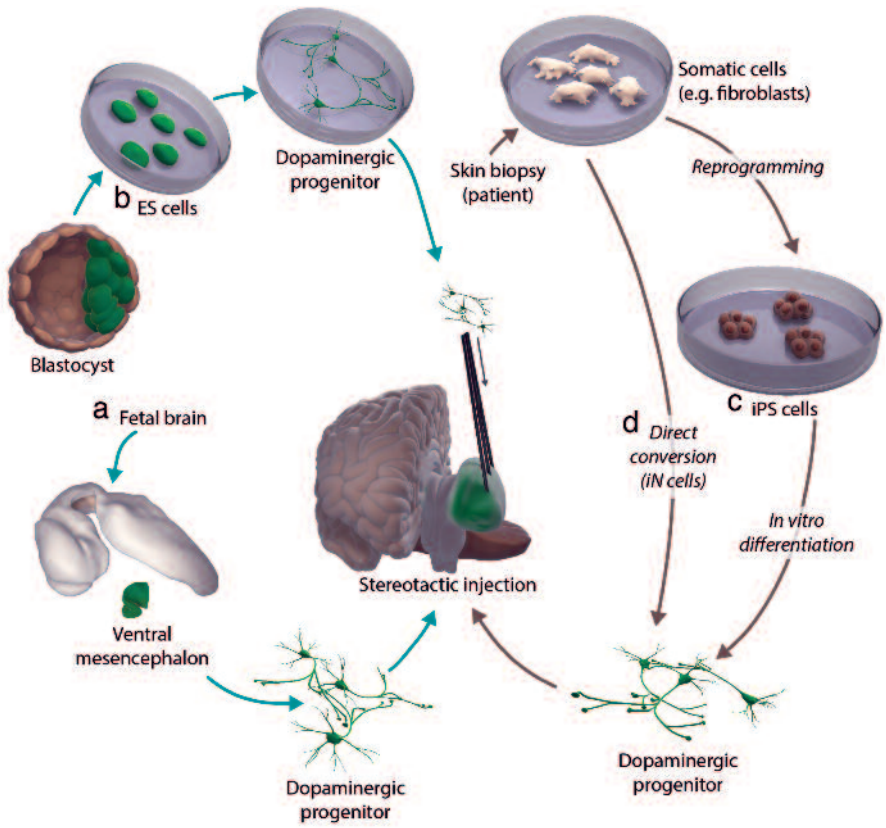
The current state – TransEuro

In order to gain an insight into what factors might determine a positive or negative clinical outcome post-transplantation, all available data from the open-label and double-blind, placebo-controlled trials were re-analysed with the aim of identifying clinical and PET-imaging variables that could identify a patient population with a better predicted outcome of this treatment.[3] After careful meta-analysis of all trials conducted, the variation in results has been mainly attributed to major methodological differences in cell preparation and trial design. In addition, tissue preparation protocols, surgical methodology, graft composition, and immunosuppression strategies were carefully compared between centres. This analysis resulted in a new clinical trial design, sponsored by the European Union (NCT01898390; www.transeuro.org.uk) with the aim to develop an efficacious and safe treatment methodology for individuals suffering from PD using foetal cell based treatments.

Cell sources of the future

However, one has to keep in mind that even though foetal cells obtained from aborted embryos (Figure 1a) can be clinically effective,[3] they are limited in availability, difficult to maintain at a high quality standard and are riddled with a number of ethical and logistical problems. In order to move to large-scale applications so that many patients can be treated, readily available, renewable cells that can be produced and stored in large quantities are needed. Thus the development of efficient protocols for the generation of midbrain dopamine neurons, from renewable cell sources, is an absolute necessity.

Figure 1 outlines the different cell sources currently being developed for clinical use. Among the different stem cell sources available, human embryonic stem cells (hESCs, Figure 1b) have advanced the most with respect to clinical application in PD. Human ESCs cells are derived from pre-implantation blastocysts. They are distinguished by their ability to self renew and to differentiate into any cell type of the body (pluripotency). hESCs can be used to obtain dopamine neurons that survive well, and that can restore functional deficits when transplanted to rodent and primate models of PD.[11,12] In 2006, the Nobel Prize was awarded to Shinya Yamanaka who demonstrated that fully differentiated cells



could be reprogrammed into an induced pluripotent stem cell (iPS, Figure 1c).[13] iPS cells are very similar to ESCs and share their characteristics of self-renewal and pluripotency. iPS cells derived from human fibroblasts can, like hESCs, be differentiated into dopamine neurons,[11] thus creating the possibility of obtaining patient specific cells for grafting. However, with both these pluripotent stem cell types there is a concern about their safety as incomplete differentiation may result in contaminating pluripotent stem cells remaining in the cell preparation that can cause tumours and overgrowths after transplantation.[14]

Recently, a new methodology for reprogramming functional dopamine neurons from skin cells has emerged[15,16] that circumvents the safety issues associated with pluripotent stem cells. The method is called direct neural conversion.[17] Here, skin cells are directly converted into functional and sub-type specific neurons without passing via a pluripotent stem cell intermediate (Figure 1d). The resulting cells, termed induced neurons (iNs) are thus a promising alternative to iPS cells for generating cells for therapy. As for iPS cells, it is possible to obtain immunologically matched cells for grafting if fibroblasts are collected from the patient themselves or from a matched donor.

When it comes to using iN cells in the clinic, several concerns related to the method for reprogramming the cells still exist. The technology makes use of lentiviral vectors and although such vectors have recently been successfully used in clinical trials,[18,19] one has to keep in mind that they integrate into the host cell genome and thus carry the ability to affect gene expression levels of endogenous genes. This in turn can lead to genomic changes that could have unwanted consequences on cell characteristics, including uncontrolled proliferation after transplantation. Therefore, before such cells can be used in a clinical trial, it is essential to establish clinically compatible reprogramming methodology in order to provide a safe and viable alternate cell source.

Ethical issues in the context of new cell sources

Stem cells and stem cell-based therapies are much observed by the media. This may create unrealistic expectations among the public, including patients and their caregivers. When stem cell research, combined with gene therapy and biobanking is taken to the clinic, many ethical issues to consider arise. This includes unique medical risks related to cell type specific issues (genetic modification, tumour risk etc. as outlined above) as well as cell processing and delivery method, and with possible conflicting requirements of traceability and anonymity.[20]

Other ethical issues concern informed consent and a number of regulatory hurdles in bringing new cell sources to the clinic. When new therapies are developed, uncertainties and gaps in knowledge make it difficult to assess risks and benefits affecting the ability to obtain a truly free and informed consent, especially for the first-in-human trials. Adequate

patient information is also a major challenge as the perspective of what is regarded as an 'effective treatment' and what risks and benefits are considered important may differ considerably between researchers, clinicians, patients and their relatives.[21,22] Furthermore, questions of access to the new treatment and issues of priority setting and financing may be raised.

The problems indicated above need to be examined and discussed, taking what is said in existing national and international guidelines as a point of departure, and updating of such guidelines whenever necessary, before we can take these therapies into the first clinical trials in humans. The successful translation of innovative stem cell therapies to the clinic will not only depend on scientific progress, but also on how we address the ethical and socio-political challenges that these treatments entail. A parallel can be drawn with the initial hope and excitement surrounding the first foetal transplants and the resulting media response when they did not turn out to be widely-replicated, or the recent controversy over the funding of human embryonic stem cell research in Europe. ◆

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July

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Interactive Metronome Adult Best Practice
13 July, 2014; London, UK
Instructor: Mary Jones OT – Sensational kids LLC and IM instructor since 2005, Nina Smith – Consultant Neurological Physiotherapist – Neuromatters Ltd
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September

36th Edinburgh Clinical Neurology Course
15-16 September, 2014; Edinburgh, UK
www.dcn...ed.ac.uk/dcn/research/training.asp or enquiries to Mrs Judi Clarke,
E. Judi.Clarke@ed.ac.uk

Parkinson's Registrar's Masterclass 26s
17-18 September, 2014; Location TBC
www.redpublish.co.uk/courses
E. info@redpublish.co.uk

International Cerebral Amyloid Angiopathy Meeting
18-20 July, 2014; London, UK
E. e.j.c.m.van_beelen@lumc.nl

Deep Brain Stimulation Masterclass Roadshows
TBC Sept/Oct, 2014 – Evening; Newcastle, UK
www.redpublish.co.uk/courses/other-courses
For further information contact info@redpublish.co.uk

7th Practical Cognition Course
25-26 September, 2014; Oxford, UK
E. events@ndcn.ox.ac.uk

ABN Autumn Meeting
30 September-1 November, 2014; Stratford, UK
E. info@theabn.org
T. 020 7405 4060

October

Coming of Age... Working in brain injury in the 21st Century
9 October, 2014; Sheffield, UK
T. 0114 250 7711
E. conference@jspsh.co.uk
www.casemanagement.co.uk/events

How Can Neuroscience Better Inform Neurorehabilitation?
16 October, 2014; London UK
T. 020 8763 2963,
www.abisolutions.org.uk
E. admin@abisolutions.org.uk

Executive Function
24 October, 2014; Ely, UK
T. 01353 652173,
E. courses@ozc.nhs.uk
www.ozc.nhs.uk

November

Parkinson's Classic Masterclass 25c
Module 2-27 November, 2014; Location TBC
For further information contact info@redpublish.co.uk

27th Annual General Meeting of the British Neuropsychiatry Association

Conference details: 27 and 28 February, 2014; London, UK. ***Report by:*** Mike Zandi, Dept of Clinical Neurosciences, Cambridge University, Cambridge, UK.

The 27th BNPA meeting, at the UCL Institute of Child Health (ICH, founded 1946), Guilford Street, Bloomsbury, brought together neuropsychiatrists, neurologists and psychiatrists in the varied themes of social cognition and impulse control, the presymptomatic treatment of Alzheimer's disease, innate autoimmunity in neurodegenerative disease and antibody-mediated CNS autoimmunity with neuropsychiatric symptoms. The meeting opened with the theme of 'new developments in cognition'.

The first three speakers discussed social cognition. David Skuse (ICH) opened the meeting and showed how oxytocin and vasopressin affect the rewarding value of social interactions. He explained one of his intentions in his recent study of common oxytocin receptor polymorphisms and their influence on face recognition memory (in family members of people with autism)[1] had been to do the same for social cognition as the famous ICH growth charts had done for height. Roland Zahn (Institute of Psychiatry) described his work in mapping the neuroanatomical correlates of moral behaviour (defined in part as both social knowledge and the motivation to act upon this knowledge), for example the neural signatures of guilt.[2] Sarah-Jayne Blakemore (UCL) described the development and neuroanatomical correlates of 'social scripts' in healthy adolescence and their eventual automation, and the remarkable influence of peer-pressures on risk taking in adolescence.[3] Eileen Joyce (UCL) presented the evidence for a 'limited general resource' of cognition in th e major neuropsychiatric condition schizophrenia.[4] The emerging and recurring theme of inflammation in neurodegenerative diseases (touched on by Nick Fox in the JNNP lecture and Catherine Slattery in a platform presentation) was introduced by James Nicoll (Southampton) who discussed the long term follow up data and far-reaching insights from the Aβ42 (Elan Pharmaceuticals) immunisation trial.[5]

The JNNP guest lecturer this year was Nick Fox (UCL) who presented the 'plausibility and perils' of the presymptomatic treatments for Alzheimer's disease, and in the design of their treatment trials.[6] He presented evidence for the 10 years of atrophy before clinical presentation in most cases, accelerating atrophy, and the promise of novel imaging techniques, including Tau-PET imaging with 11 C-PBB3. This excellent lecture is available on-line courtesy of the JNNP: http://goo.gl/95sVXB. The junior members' platform presentations were of a high quality and covered an analysis of the innate immunity microglial-expressed gene TREM2 and its variants in Alzheimer's Disease and other dementias (Catherine Slattery, UCL), a case control study of post-ictal psychosis (Georgy Pius, Salford), and the association between joint hypermobility, autonomic hyperactivity and neurodevelopmental disorders (JA Eccles, Brighton).

In the research update, David Okai (Institute of Psychiatry and Oxford) reviewed Impulsive Compulsive Behaviours in Parkinson's disease, and the evidence for cognitive behavioural therapy.[7] Hugh Rickards (Birmingham) presented a review and personal view on the efficacy of cholinesterase inhibitors in a range of neuropsychiatric disorders, highlighting the deficits in many of the trials and meta-analyses to date.

The neuropsychiatric manifestations of inflammatory brain diseases and encephalitis were the themes of the second day. Neil Scolding (Bristol) gave an overview on the approach to diagnosing inflammatory CNS diseases, focusing on CNS vasculitis (including amyloid related angiitis), CNS lupus, Behçet's disease and neurosarcoidosis. He emphasised the importance of excluding mimics and retaining general medical knowledge relevant to recognising multi-system diseases, and the importance of neuropathology in making a diagnosis.[8] Jeremy Isaacs (National Hospital for Neurology and Neurosurgery), surveyed the field of 'the old and the new' paraneoplastic syndromes – including illustrative vignettes of CV2-antibody associated chorea and Ma2 antibody associated hypersomnolence – and the role of PET imaging in looking for tumours.

Tom Solomon (Liverpool) presented illustrative cases of CNS infections with psychiatric presentations: subacute sclerosing panencephalitis, HSV encephalitis (with NMDAR antibody mediated 'relapses', HIV dementia, TB meningitis and syphilis. In the BNPA Medal Lecture, Angela Vincent (Oxford) gave an update on the novel cell surface antibody CNS syndromes, introducing some novel antibodies, and how these syndromes have expanded to include those with psychiatric presentations, in particular the NMDAR encephalitis syndrome.[9]

A highlight of the meeting, in the final afternoon, was the Wellcome Trust Debate: 'this house believes that neurology and psychiatry should be one medical discipline'. Chaired by Peter White (QMUL), the motion for was argued by Geraint Rees (@profgeraintrees, UCL) and Joel Winston (@Joel_Winston, UCL), and the motion against by Simon Wessely (@WesselyS, IOP) and Ben Robinson (@psych_trainees, Maudsley). In the final analysis, 68 members of the audience voted for the motion, 60 against, and 3 abstained. The debate and ensuing discussion were entertaining and provocative. Ideological and philosophical concerns were pitted against the pragmatics of professional organisation and service delivery, though all were agreed that cross-over training was a good thing for trainees in psychiatry and neurology and that the means should be available now for this to happen.[10]

This was an enjoyable event, with a warm atmosphere and lots of discussion in the coffee breaks. Twenty four posters covered the above and other themes, including musical hallucinations and functional disorders. At the conference dinner at the Magic Circle, near Euston, we were treated to a tour of the museum by magician and pickpocket ('Man of Steal') James Freedman, who demonstrated the art of controlling and directing our attention. Podcasts from interviews with some of the speakers are continuing to appear on the JNNP website: http://feeds.bmj.com/jnnp/podcasts ◆

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European Pain Federation (EFIC) Annual Congress

Conference details: 9-12 October, 2013; Florence, Italy. ***Report by:*** Susan Mayor PhD, Medical Writer, London, UK.

More than 4000 physicians, researchers and specialist nurses and psychologists gathered in the beautiful medieval city of Florence to exchange latest research findings and clinical insights on acute, chronic and recurrent pain management at the eighth Pain in Europe Congress. Held every two years and hosted by the European Pain Federation EFIC, a multidisciplinary group of members of national pain societies throughout Europe, the meeting provides an excellent opportunity to keep up-to-date with pain research, with scientific sessions and poster presentations covering a wide range of topics from biomolecular science to interventional pain practice.

Chris Wells, Consultant in Pain Relief, Liverpool, UK, chaired the first plenary session, which included a fascinating review of the mechanisms underlying visceral pain given by Fernando Cervero, from the Anaesthesia Research Unit at McGill University, Montreal, Canada. Ben Seymour, from the University of Cambridge and the Center for Information and Neural Networks, Osaka, Japan, gave a detailed update on systems level models for the neural basis of pain motivation systems and Maree Smith, Head of the Pain Research Group, University of Queensland, Brisbane, Australia, took delegates on a whistlestop tour of pain pharmacogenetics, explaining variations in individual responses to medication.

'Respect opioids but don't fear them' was the message from several topical discussions of the use of opioids for non-malignant pain, balancing their efficacy in pain relief against abuse potential and emphasising the need for careful review systems to ensure patients are treated safely. More than 1200 poster presentations provided additional updates from new pain research and clinical studies, and networking continued over a conference held at the splendid Palazzo Vecchio held in the imposing Salone dei Cinquecento dating from 1494.

European survey reveals lack of undergraduate pain education

Fewer than one in three undergraduate medical schools across Europe have dedicated teaching on pain assessment and management, report results from the first European-wide survey to assess pain education.

An expert taskforce from the European Pain Federation carried out a cross-sectional survey on pain education using publicly available undergraduate medical curriculum for 242 of the 249 medical schools in 15 European countries. They also commissioned telephone interviews with staff from medical schools in 10 of these countries.

"There is a striking lack of dedicated teaching on pain in undergraduate medical courses across Europe, with the exception of medical schools in France and a handful of schools in other countries," reported Emma Briggs, lecturer and King's teaching fellow at King's College London, UK, chair of the British Pain Society Education Special Interest Group and a member of the APPEAL (Advancing the Provision of Pain Education and Learning) project taskforce.

Results showed that 69% of undergraduate medical schools had no dedicated teaching on pain as part of the curriculum. An even higher proportion (82%) had no dedicated compulsory teaching on pain, and medical schools generally reported very low attendance at non-compulsory courses.

Even in medical schools providing dedicated, compulsory teaching on pain, medical students were receiving only 12 hours teaching, which accounted for only 0.2% of their total taught hours, on average.

"A lack of knowledge about pain among physicians has long been recognised as a key barrier to effective pain management," said Professor Hans Kress, president of the European Pain Federation. "This survey has shown it's very likely that medical schools are not covering pain adequately," agreed Professor David Gordon, president-elect of the World Federation for Medical Education.

The exert taskforce is recommending:

- Establishing a European framework for pain education to improve the consistency of pain teaching among medical schools.
- Introducing compulsory pain teaching for all undergraduate medical students.
- Improving the documentation of pain teaching with clearly stated content and student competencies in pain management.

The APPEAL study was supported by logistical and editorial assistance funded by Mundipharma International Limited.

Norwegian study shows one in ten people have chronic widespread pain

More than one in ten people have chronic widespread musculoskeletal pain, shows a large population cohort study, which suggests an association with anxiety, depression and insomnia.

Few studies have previously assessed psychosocial and lifestyle factors and the risk of developing chronic widespread musculoskeletal pain. Norwegian researchers investigated this with a population-based cohort of 28,367 people aged 19-86 years taking part in the Norwegian Nort-Trøndelag Health Study (HUNT). None of them had chronic widespread musculoskeletal pain – defined as pain at three or more predefined sites (involving trunk, arms and legs) for at least three months in the last year - at the start of the study in 1995-97.

When patients were reassessed after 10 years in 2006-2008 just over one in ten reported chronic widespread musculoskeletal pain. Symptoms of anxiety and depression (assessed with the 14-item Hospital Anxiety and Depression Scale) were associated with increased risk of this pain, as was insomnia and having a body mass index > 25 kg/m2. Smoking also increased risk.

The research group found that moderate exercise and education were protective factors for chronic widespread musculoskeletal pain. Alcohol use was associated with a marginally reduced risk. They concluded, " The study results indicate a possible influence of psychosocial and lifestyle factors on the long-term risk of chronic widespread musculoskeletal pain.

Multidisciplinary pain management programme optimises opioid use

Attending a four-week multidisciplinary pain management programme was associated with a one-third reduction in dose of opiate pain medication in patients with chronic non-malignant pain in an observational study.

Researchers from the Pain Management Centre at St Thomas' Hospital in London, UK, set out to investigate whether attending an inpatient pain management programme could optimise patients' use of opiate pain medication. They had previously seen this as a secondary finding in an audit carried out several years ago. To study this further they prospectively followed-up 125 patients attending their inpatient pain management programme during a one-year period.

All of the 125 patients took opiate medication before attending the pain management programme, with a mean equivalent daily dose of morphine of 40.89mg (95% confidence interval 20.77 to 61.00mg). This fell by 32% to a mean of 28.00mg at the end of the four-week multidisciplinary pain management programme. This reduction in opiate use was sustained at 9 months follow-up (mean equivalent daily dose 25.41mg (95% CI 12.59 to 38.24mg), representing a 38% reduction from before the programme.

Results also showed a reduction in the daily dose of non-steroidal anti-inflammatory drugs, total number of drugs and number of classes of drugs taken by patients in the study.

Lead author C. Stack, from St Thomas' Hospital, London, concluded, " Completing a four-week inpatient multidisciplinary pain management programme incorporating pain management principles within a cognitive behavioural framework was associated with a 32% reduction in opiate pain medication use, which was sustained out to nine months." ◆

The next European Pain Federation EFIC Congress will take place on 2-5 September 2015 in Vienna, Austria, with the theme of translating evidence into practice. More information at http://www.kenes.com/efic2015/

IIH – The unknown known

Reviewer: Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge University, UK.

Despite the frequency at which clinicians encounter patients with Idiopathic Intracranial Hypertension (IIH) in everyday clinical practice, there has been no large prospective double-blind, placebo controlled trial on treatment options performed to date. Consequently, there has been a failure to establish consensus guidelines regarding medical management with diuretics, and the optimal timing of surgical intervention (be it shunt or optic nerve sheath decompression) remains ambiguous. Current guidelines that exist are principally derived from retrospective series and anecdotal evidence, so a trial of this nature has been long overdue.

The NORDIC research group enrolled 165 patients in a study from 38 different institutions in North America, and published the clinical profile of these patients at baseline in a recent issue of JAMA Neurology, with trial results to be published in a follow-up article. The aim of the study is to establish whether patients with IIH and mild visual loss will benefit more from a weight loss regime alone, or a weight loss programme in combination with acetazolamide. Their eligibility criteria was strict – including only patients who met the modified Dandy criteria for IIH. Perhaps unsurprisingly, the cohort consisted almost exclusively of women (98%), and the majority of participants were obese (88%) with an average BMI of 40. This strong female preponderance is a reminder of the fact that men purported to have this condition should be exhaustively investigated for other secondary causes of elevated intracranial hypertension. In line with other retrospective studies, headache was the presenting symptom in 84% of cases. Transient visual obscurations occurred in 68% of this cohort, with a median incidence of one per day. Only 32% reported visual loss. Pulse synchronous tinnitus was reported by just over a half of patients. Interestingly, there was also a high prevalence of back pain in this cohort (53%), and the mechanism is postulated to be due to filling of spinal dural root sheaths by CSF under high pressure.

Almost 1 in 5 patients reported double vision but the prevalence of esotropia found on exam was much lower, possibly as many patients may only have transient sixth nerve dysfunction as a consequence of their elevated intracranial pressure. The most common perimetric finding was a partial arcurate visual field deficit with an enlarged blind spot. The mean opening pressure on lumbar puncture was 343.5 mm H2O (range between 210 and 670 mm H20) and did not correlate with BMI or the degree of visual field loss on perimetry.

Future published results from this unique prospective trial are eagerly anticipated, as they will provide us with more definitive answers on the best therapeutic management for IIH – clarifying the role of weight loss in the management of IIH both alone and in combination with diuretics. Hopefully it will also serve as an impetus for further multicentre studies enrolling IIH patients with moderate or severe visual loss at presentation.

The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. Wall M, Kupersmith MJ, Kieburtz KD et al. JAMA Neurol. 2014 Jun 1;71(6):693-701.

FTD GWAS – Finding a signal in the noise

Reviewer: Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge University, UK.

When I hear the term frontotemporal dementia, I am reminded of the first patient I met with this condition while working as a neurology registrar in Dublin. This patient's wife had originally brought him to the GP as she was bewildered by the fact that her previously conservative 56 year old husband had taken to wearing a clown mask in the local supermarket and pinching strangers. It subsequently emerged that he had a mutation in the tau gene, which along with mutations in progranulin and C9orf72, is a common gene associated with hereditary FTD. As well as the behavioural variant seen in this patient, there are language variants of FTD and it can also co-occur with motor neuron disease (FTD-MND).

In a bid to identify novel genetic risk loci associated with the non-familial variety of FTD, Ferrari and colleagues collaborated to perform a genome-wide association study which analysed samples from 3526 patients with FTD and 9402 healthy controls. This is the largest GWAS for FTD performed to date, and the results are published in July's Lancet Neurology. Notably, the researchers discovered a new potential locus on chromosome 11 encompassing the RAB38/CTSC genes, which was suggestive for the behavioural FTD subtype. Both these genes are involved in lysosomal biology, which could be linked to the autophagy processes in FTD. The HLA locus on chromosome 6 was statistically significant for the entire cohort, and opens up the possibility that inflammatory processes are involved in the pathogenesis of FTD. This HLA locus will already be familiar to those working in the field of MS, PD and Alzheimer's disease, and lends further support to the hypothesis that the immune system plays a role in a diverse spectrum of neurological disorders. These new insights into the genetic architecture of FTD suggest a number of useful directions for future functional studies.

Ferrari R, Hernandez DG, Nalls MA et al. Frontotemporal dementia and its subtypes: a genome-wide association study. Lancet Neurol. 2014 Jul;13(7):686-99.

Good with faces. Treating prosopagnosia

Reviewer: Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge University, UK.

Prosopagnosia is an impairment in the ability to recognise faces and can be developmental as well as acquired through brain injury. One of the tell-tale signs of the condition is an overareliance on cues such as situational context, hair, gait, clothes and voice to identify others. It is commoner than one might expect, affecting an estimated 2.5% of the population. The neurologist Oliver Sacks has written extensively on the condition, and describes himself as having "moderate" developmental prosopagnosia. Imaging studies have indicated that patients with this condition have volume reductions in areas associated with face processing in the right fusifom gyrus and inferior temporal gyrus. Although it is generally regarded as being untreatable, recently various research groups have endeavoured to develop rehabilitation programmes to enhance facial recognition. One of the more promising of these studies was published recently in "Brain". Joseph DeGutis and colleagues recruited 24 patients with developmental prosopagnosia and had them perform a 3–week online face-training programme targeting holistic face processing. Although the cohort of patients they trained was small, the study was well-designed, and their results suggested that face recognition abilities may be at least partially remediable to this type of cognitive training. Whilst it is always challenging to accurately characterise how well this type of training translates from the "lab" into patients "everyday" face recognition abilities, the patients in this study kept self-reported diaries to document real-world improvements, and showed modest but consistent benefits. Investigating whether or not these benefits acquired from training are sustainable in the long-term, and if this type of training can be used by people with acquired prosopagnosia, are interesting potential avenues for future research.

Holistic face training enhances face processing in developmental prosopagnosia. DeGutis J, Cohan S, Nakayama K. Brain. 2014 Jun;137 (Pt 6):1781-98.