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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. 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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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Cover picture courtesy of ABI Solutions. See advert (left).

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Mike Zandi, Editor.

In this issue we have articles that cover the latest advances in the mechanisms and potential therapy of prion disease and Parkinson's disease to clinical articles with applications of the latest science for trigeminal autonomic cephalalgias, spinal cord dysraphism, rehabilitation approaches for Charcot-Marie Tooth disease and oral therapies in multiple sclerosis. We have an Association of British Neurologists Trainees (ABNT) article provided by Emma Tallantyre and Helen Devine who dissect the Shape of Training Review and Proposals – which have generated much debate in the last year – and how the proposals may influence neurology training.

Our first review article in this is issue is from Giovanna Malluci and Nicholas Verity who write an update on the pathophysiology of prion disorders. They focus on their own remarkable work which has demonstrated the central role of the Unfolded Protein Response in the disease, and how selective inhibition of the PERK-eIF2α-P signalling pathway in the process by a small molecule can be neuroprotective through restoring protein translation, even after disease onset. Our second review article, by Lilia Dimitrov and Ben Turner, the second in their trio of papers on oral therapies for relapsing remitting MS, introduces us to the pyrimidine synthesis inhibitor teriflunomide, through the TEMSO, TOWER and TENERE trials, including the expected efficacy and side effects to be aware of.

For our headache article, Anna Cohen provides a useful and detailed up-to-date summary of the clinical features, pathophysiology and pharmacological and non-pharmacological therapies for the trigeminal autonomic cephalalgias. Tom Foltynie and Dilan Athuda take us through the very latest in ongoing studies into neuroprotective and neuroregenerative agents in Parkinson's Disease, including repurposed therapies. Calcium antagonism and uric acid are but two approaches gleaned from epidemiological studies, and the range of clinical trials underway is promising. Michael Serada and colleagues from Göttingen, review the evidence for rehabilitation in Charcot-Marie Tooth disease type 1, dealing with the issue of overwork fatigue, creatine and ascorbic acid treatments and skin-derived biomarkers. Finally Ruth-Mary deSouza and colleagues from KCL, Chicago and Toronto discuss the tethered cord syndrome and spinal cord dysraphism and their management in our neurosurgical article. As ever we include reviews of recent scientific papers and conferences, courses and books, and welcome suggestions for and submissions to the journal.

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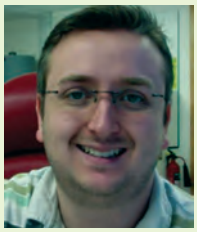
Update on the Pathophysiology of Prion Diseases

Giovanna Mallucci
is Professor of Neuroscience and Programme Leader at the MRC Toxicology Unit and Honorary Consultant Neurologist at Addenbrooke's Hospital, with a specialist interest in dementia. She gained her PhD in 2001 from Imperial College, London, developing a new transgenic model of 'reversible' prion disease, after which she combined scientific and clinical careers focused on understanding generic mechanisms of neurodegeneration.



Nicholas Verity
is a PhD student at the MRC Toxicology Unit in Leicester. He is primarily interested in translational changes in the brain during the course of neurodegenerative diseases.

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The authors declare no conflict of interest.

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Summary

- Prion diseases are characterised by the accumulation of misfolded prion protein (PrP) and widespread neuronal loss throughout the brain. Recent work has elucidated a major mechanism by which misfolded PrP induces neurodegeneration in prion disease.
- Rising levels of misfolded PrP lead to sustained dysregulation of an endogenous cellular pathway, the unfolded protein response (UPR), which regulates protein synthesis at the level of translation initiation.
- This results in the sustained reduction in global protein synthesis rates in neurons, leading to loss of critical proteins, resulting in synaptic failure and neuronal death.
- Genetic and pharmacological manipulation of this pathway to restore protein synthesis prevents neuronal loss, reverses cognitive deficits and abrogates clinical disease.
- The same branch of the UPR is over-activated in other protein misfolding disorders, including Alzheimer's and Parkinson's diseases, ALS and PSP. Further, it is a key pathway in learning and memory. Therefore, UPR modulation to restore protein synthesis levels in neurons is potentially an important new therapeutic strategy for neurodegenerative disease.

Background

Prion diseases are rare neurodegenerative disorders that belong to the emerging group of protein misfolding diseases, which includes Alzheimer's and Parkinson's diseases. In each case, the accumulation of a disease specific protein is associated with a relatively stereotyped clinicopathological syndrome. How neuronal loss occurs in these disorders is not clear, but recent work has revealed the mechanism by which protein misfolding leads to neurodegeneration in prion disease.

The central pathogenic process in prion disorders is the formation and accumulation of an aberrantly folded conformer (PrP^{Sc}) of the host-encoded cellular prion protein (PrP^{C}).[1] PrP^{Sc} is generated from PrP^{C} through an autocatalytic post-translational change in secondary structure (Figure 1).[2] The misfolded protein aggregates and accumulates throughout the brain, is accompanied by astrocytosis, spongiform change and extensive neuronal cell loss. Whilst PrP^{Sc} is associated with infectivity (prion diseases are transmissible), there is extensive evidence that it is not in itself neurotoxic. Sub-clinical states of prion disease have been identified in which extensive accumulation of PrP^{Sc} is dissociated from neurotoxicity.[3] PrP^{Sc} is harmless to cells devoid of PrP^{C}, and therapeutic agents targeting PrP^{Sc} have very limited efficacy and do not prevent neuronal loss. PrP^{C} is absolutely required for susceptibility to prion neurotoxicity: PrP-null mice are resistant to prion disease[4] and depleting PrP^{C} in neurons of prion infected mice cures disease, as conversion can no longer occur.[5] Thus, the process of prion protein misfolding is central to neurotoxicity. Recent work has shown that neuronal death results from dysregulation of the cellular response to unfolded proteins triggered by the process of prion protein misfolding.[6]

The Unfolded Protein Response

All cells need correctly folded proteins for normal functioning. The build up of unfolded proteins within the endoplasmic reticulum (ER) constitutes a form of cellular stress that elicits a protective signalling cascade, the Unfolded Protein Response (UPR), which maintains protein-folding homeostasis, "proteostasis".[7] Rising levels of misfolded proteins in the ER are detected by Binding immunoglobulin protein (BiP), which results in activation of the three branches of the UPR to increase protein folding through chaperone expression (via ATF6 and IRE1 branches) and to transiently reduce protein levels by inhibiting protein synthesis (PERK branch). This occurs via the phosphorylation first of PERK and then of the alpha subunit of eIF2 (eIF2α), which is needed for formation of ternary complex and initiation of translation. Activation of the UPR is usually a transient event that terminates when eIF2α-P is dephosphorylated by GADD34, rapidly restoring protein translation.[8]

The UPR in prion disease

Recent work in prion diseased mice revealed that rising levels of misfolded prion protein caused and sustained increase in the phosphorylation of PERK and eIF2α in neurons.[6] The effect of this is the sustained reduction in global protein synthesis rates in neurons, causing catastrophic decline in levels of key proteins including synaptic proteins, vital for healthy functioning and neuronal survival. The result is neurodegeneration. Genetic manipulation of the pathway to reduce levels of eIF2α-P restored vital protein synthesis rates and was profoundly

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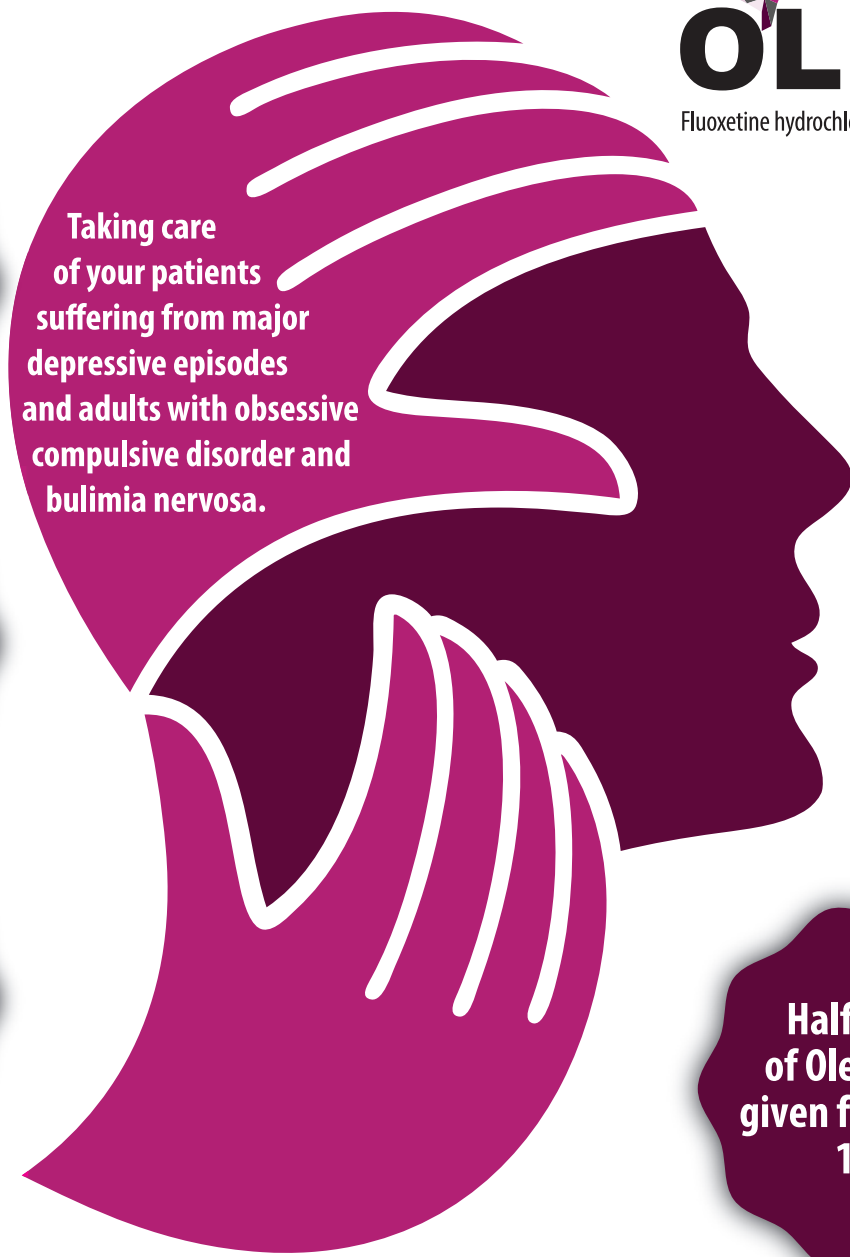

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Adverse events should be reported to the local regulatory authority. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Amdipharm Mercury Medical Information via telephone on 08700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

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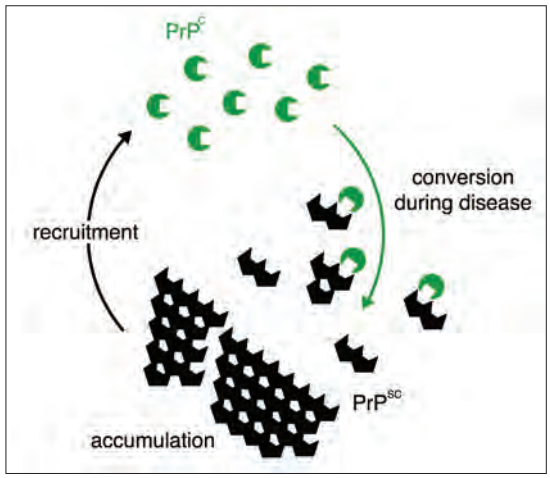

Figure 1: Schematic of prion conversion.
Native prion protein (PrP^{C}; green partial circles) is converted into PrP^{Sc} (black partial hexagons) in an autocatalytic process during prion replication. It is likely that PrP^{Sc} seeds (multimers) interact with individual PrP^{C} molecules. The two proteins have identical primary structure but differ in secondary structure: PrP^{C} is predominantly alpha helical whereas PrP^{Sc} is rich in beta-sheet, protease resistant and accumulates, recruiting more PrP^{C} for further cycles of conversion.

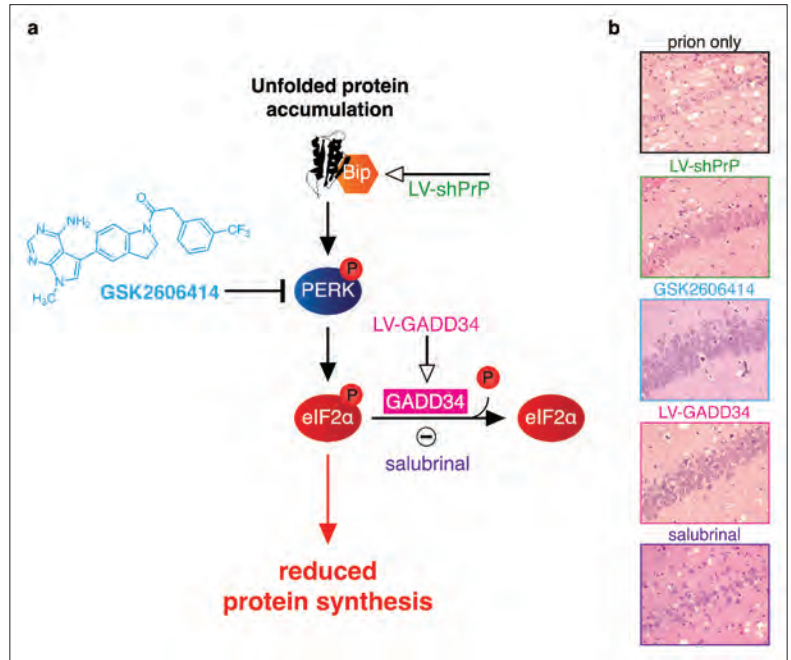

Figure 2: Schematic representation of PERK branch of the Unfolded Protein Response (UPR) leading to translational repression, points of intervention and neuroprotective effects. a, increasing levels of misfolded proteins are detected by BiP in the ER, activating PERK, which autophosphorylates and in turn phosphorylates eIF2α, resulting in reduced protein synthesis. The points of action of GSK2606414 (a specific inhibitor of PERK), of LV-shPrP (lentivirus mediating RNAi of PrP), of LV-GADD34 (lentivirus over-expressing the eIF2α-P phosphatase, GADD34) and salubrinal (prevents dephosphorylation of eIF2α-P, exacerbating the reduction of translation) are shown. b, Haematoxylin and eosin stained sections of CA1 region of hippocampi from mice treated with lentiviruses mediating RNAi of PrP and GADD34 over-expression; with PERK inhibitor GSK2606414, and salubrinal. Inhibition of UPR-mediated translational shutdown by shPrP, GADD34 and GSK2606414 results in marked neuroprotection with normal thickness of the neuronal ribbon. In contrast, worsening of neurodegeneration is seen with salubrinal, which inhibits the restoration of translation. (Adapted from [6, 10]).

neuroprotective (Figure 2). This was true for upstream (knockdown of PrP levels) or downstream (by lentivirally mediated overexpression of the eIF2α-P phosphatase GADD34) interventions that reduced eIF2α-P levels. The resultant rescue of protein synthesis rates prevented decreases in synaptic protein levels, maintained synapse number and synaptic function, preventing behavioural and cognitive deficits, and resulted in extensive neuroprotection. Most importantly, there was a significant increase in survival. Notably, inhibiting the dephosphorylation of eIF2α-P with the small molecule salubrinal, had the opposite effect, exacerbating the decrease in protein synthesis and accelerating disease. Critically, this rescue occurs downstream of prion replication and independently of it. PrP^{Sc} levels are unaffected.

Pharmacological modulation of the UPR in prion disease

These data led to the prediction that pharmacological inhibition of PERK- eIF2α-P signalling would be similarly neuroprotective. GSK2606414, a highly selective PERK inhibitor,[9] was orally administered to prion-infected mice daily from points both before and after the onset of behavioural deficits.[10] PERK inhibition by GSK2606414 similarly prevented elevated levels of eIF2α-P and decline in protein synthesis rates and resulted in extensive neuroprotection throughout the brain. Encouragingly, treatment that was started even after the emergence of cognitive deficits had the same beneficial effects as treatment from earlier time-points. This work was the first description of a small molecule able to prevent neuronal loss and clinical disease in vivo.

Wider relevance

There is increasing evidence that UPR dysregulation is a central process in protein misfolding neurodegenerative diseases, and that maintaining translation levels is essential for neuronal health. Increased PERK-P and eIF2α-P have been reported in post-mortem analyses of brains of patients with AD, PD, ALS, and the tauopathy progressive supranuclear palsy (PSP), as well as prion disease.[11] Genetic polymorphisms in PERK pre-dispose to PSP.[12] The pathway is also implicated in learning and memory; manipulation of eIF2α-P levels boost cognition in wild type mice and restore memory deficits in AD mouse models. Thus, it would appear that targeting UPR dysregulation that occurs downstream of misfolded protein replication, be this prion, amyloid beta, tau, α-synuclein or TDP-43 may hold promise for new treatments for neurodegenerative disorders more broadly. ◆

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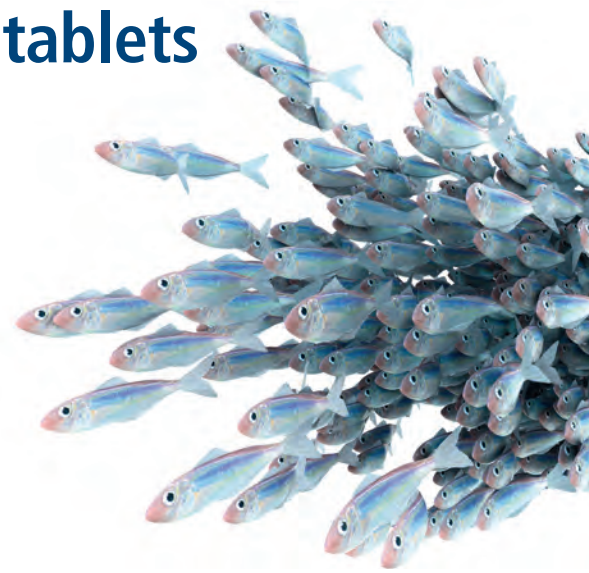

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Oral therapies in relapsing remitting multiple sclerosis – Part 2

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Teriflunomide

Introduction

In the first of this 3-part series of articles, we looked at the first oral therapeutic for relapsing-remiting multiple sclerosis (RRMS) to gain approval – the sphingosine-1-phosphate receptor modulator fingolimod. Teriflunomide became the second oral therapy approved by the EMA in 2013. In January 2014 NICE recommended Teriflunomide for treating adults with active RRMS only if they do not have highly active or rapidly evolving severe (RES) RRMS.[1] Teriflunomide is a once a day tablet, derived from leflunomide which has been used extensively in rheumatology. Teriflunomide has undergone an extensive trial development with three pivotal phase III studies examining both 7mg and 14mg dose, in Europe the licenced dose is 14mg.

Mechanism of Action

Teriflunomide, a *de novo* pyrimidine synthesis inhibitor, is the primary metabolite of leflunomide which has been used worldwide as an oral disease modifying drug in the management of rheumatoid arthitis since 1998.[2] Although the mechanism of action is not fully understood, teriflunomide is believed to have both anti-inflammatory and anti-proliferative actions mediated via reversible inhibition of the mitochondiral enzyme dihydroorotate dehygrodenase (DHO-DH).[3] This enzyme is needed for the de-novo synthesis of pyrimidines in actively dividing cells, particularly proliferating lymphocytes.

Rapidly absorbed with maximum concentrations achieved after 12 hours, teriflunomide is metabolically stable with a long half-life of 10-12 days.[4-5] It undergoes metabolism primarily via hydrolysis with a small component via oxidation. Clinical data suggests that the majority of elimination is of unchanged product via faeces, followed by elimination of the metabolite 4-trifluoromethylaniline (TFMA) oxalinic acid via urine.[6] As teriflunomide may remain detectable in the serum for many months after stopping treatment, elimination can be accelerated using a course of activated charcoal or cholestyramine. This may be used for women wishing to become pregnant and clearance of teriflunomide can be confirmed by measuring serum levels. 99% of the compound is protein bound (indicating high potential of drug interaction) however teriflunomide is not metabolised by cytochrome P450 (CYP).[4]

Clinical Efficacy

There have been three pivotal Phase III, international, multi-centre trials in the development programme of teriflunomide for RMMS; two placebo-controlled studies TEMSO and TOWER and the active-controlled TENERE that compared teriflunomide to injectable IFN-b (Rebif™).[7-9] TEMSO, TOWER and TENERE each contained two teriflunomide arms at a daily dose of 7mg or 14mg. Only the results of the licensed dose – 14mg – will be presented here.

TEMSO contained 1088 patients over a study duration of 108 weeks.[7] Annualised relapse rate (ARR) was the primary endpoint of the study with the results showing a relative risk reduction in relapses of 31.5% for the 14mg group compared to placebo (0.37 versus 0.54, $p<0.001$). The principle secondary end point of confirmed disease progression for at least 12 weeks was also significantly reduced for the teriflunomide arm compared to placebo (20.2% versus 27.3%, $p\leq0.05$). MRI findings were encouraging with a 67.4% smaller change from baseline in total lesion volumes compared to placebo (+0.72 versus +2.21, $p<0.001$), fewer Gd-enhancing lesions on T1-weighted scans (0.26 versus 1.33, $p<0.001$) and fewer unique active lesions (0.75 versus 2.46, $p<0.001$). In contrast however, brain atrophy data found no difference between placebo and either teriflunomide arm.

TOWER contained 1169 participants from 26 countries but in this case treatment duration was variable with a range between 48-152 weeks.[8] Again the primary end point of ARR was used and a relative risk reduction of 36.3% was found for the teriflunomide arm when compared with placebo; (0.32 versus 0.50, $p=0.0001$). The main secondary endpoint was the time to sustained disability progression (defined as an increase in EDSS score by 1 point for at least 12 weeks) and only just achieved significance for the 14mg arm with a risk reduction of 31.5% compared to placebo (Hazard ratio versus placebo 0.68, $P<0.05$).

TENERE involved a smaller participant group of 324 patients over the course of 48-118 weeks.[9] In contrast to the other studies discussed so far, treatment failure (defined as first confirmed relapse or permanent study discontinuation) was the primary outcome measure with no difference between teriflunomide 14mg versus IFN-b. For the secondary endpoint, ARR, there was no signficant difference between IFN-b and 14mg teriflunomide (0.22 and 0.26 respectively, $p=0.60$). Other secondary outcomes included fatigue as measured by the Fatigue Impact Scale and patient satisfaction and both were found to be signficantly improved in those allocated to teriflunomide compared to IFN-b.

Safety

Throughout the entire teriflunomide MS development programme (placebo controlled trials and their extensions), a total of 2284 patients have been exposed to teriflunomide at either 7mg or 14mg with a maximum exposure of 11.1 years. There have been 13 deaths; 5 occuring during the placebo-controlled trials and 8 during the extension studies. No evidence indicates teriflunomide as the causative agent.[10]

Table 1: Summary of 14mg teriflunomide efficacy across Phase III clinical trials

Clinical outcome	TEMSO (n = 1088, 108 weeks)		TOWER (n = 1169)		TENERE (n = 324)	
	Teriflunomide 14mg	Placebo	Teriflunomide 14mg	Placebo	Teriflunomide 14mg	IFN-b-1a
Annualised relapse rate - p value	0.37 <0.001	0.54 NA	0.32 <0.001	0.50 NA	0.26 0.60	0.22
Confirmed disability progression for a duration of ≥12 weeks (%) - p value	27.3 <0.05	20.2 NA	NA NA	NA NA	NA NA	NA
Absence of disability progression during study duration at 108 weeks (%) - p value	56.5 <0.01	45.6 NA	84.2% <0.001	80.3% NA	NA NA	NA NA
Cumulative percentage of estimated failures at 48 weeks (%)	NA	NA	NA	NA	33	37
Mean no. Gd+ lesions - p value	0.26 <0.001	1.33 NA	NA	NA	NA	NA
Mean no. of unique active lesions - p value	0.75 <0.001	2.46 NA	NA	NA	NA	NA
Mean brain volume change (%) - p value	-0.003 0.35	-0.004 NA	NA	NA	NA	NA

In both TOWER and TEMSO adverse events occurred at a similar rate across the teriflunomide and placebo groups with 82% of those in the placebo group reporting at least one adverse event compared with 84% in the 14mg teriflunomide arm (TOWER).[8] The corresponding values in TEMSO were 87.5% and 90.8%.[7] Serious adverse events in TOWER occurred at an equal rate with 12% of partipants reporting them in the placebo and 14mg teriflunomide groups.[8] A higher rate of serious adverse events were found in those taking teriflunomide in TEMSO with 15.9% compared to 12.8% in placebo.[7]

The most frequent treatment-emergent adverse events found in a pooled analysis of all the placebo-controlled Phase II/III studies include headache, Diarrhoea, nausea, raised ALT and alopecia.[11]

Leucopenia (neutropenia and lymphopenia) was found across all studies but this never exceeded 15%, importantly was not correlated with infection and resolved on discontinuation.[10] Serious infection occurred in 2.5% of participants in both placebo and 14mg groups with nasopharyngitis accounting for most of the cases. Two serious opportunistic infections were reported in TOWER; a case of intestinal tuberculosis (teriflunomide 14mg) and a case of hepatitis C with cytomegalovirus (placebo).[10]

Patients taking teriflunomide were more likely to experience rises in blood pressure (both systolic and diastolic measures) particularly affecting those with baseline hypertension indicating need for concomitant blood pressure monitoring.[10] The aetiology of this is uncertain as there are no obvious effects of the drug on the kidney, vasoconstriction, increased heart rate or fluid retention. No instances led to study discontinuation.

Peripheral neuropathy was also reported at higher rates within the treatment groups, with 10 cases in TEMSO and 18 in TOWER encompassing both mononeuropathies and polyneuropathies with no reported cases in placebo groups.[10] It is however difficult to determine cause and effect within this clinical population group due to the nature of the disease process.

Teriflunomide has been found to be fetotoxic in animal studies. There have been 81 pregnancies throughout the clinical programme with available data on 66.[11] Of these, 23 were healthy pregnancies, 12 spontaneous and 26 induced abortions and 5 ongoing pregnancies. There is a long 'washout' period, with two drug-free years required before women can conceive. On a related note, consideration to type or dose of oral contraceptive should be used as teriflunomide been found to increase the exposure to ethinylestradiol and levonorgestral.[12]

Long-term clinical data does not indicate an increase in either haematological and solid tumour malignancies above the population level.[13]

Adverse events during treatment leading to treatment discontinuation were higher in the teriflunomide arm compared to placebo across both TEMSO (10.9% versus 8.1% respectively) and TOWER (16% versus 6%).[7-8] However, overall a greater proportion of patients in the placebo arms discontinued treatment compared to the active arms in both TEMSO (29% versus 27%) with the reverse seen in TOWER (32% versus 34%).[7-8] In the active comparator study TENERE, 22% of those on IFN-b discontinued treatment permanently due to adverse events compared to just 12% in the teriflunomide 14mg group. So although data from the clinical trials suggests that IFN-b is clinically equivalent to teriflunomide 14mg, this data suggests that the latter is associated with better tolerance of side effects. ◆

Box with Monitoring recommendation for teriflunomide

Before treatment

- Full blood count, including white blood cell differential and platelet count.
- Liver function tests, in particular alanine aminotransferase.
- Blood pressure

During treatment

- Full blood count if clinical need indicated.
- Liver function tests every 2 weeks for the first 6 months of treatment, then every 8 weeks thereafter.
- Blood Pressure

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Trigeminal Autonomic Cephalalgias

A Diagnostic and Therapeutic Overview

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The Trigeminal Autonomic Cephalalgias (TACs) are a group of headache disorders characterised by attacks of moderate to severe unilateral pain in the head or face, with associated ipsilateral cranial autonomic features such as lacrimation, conjunctival injection, rhinorrhoea, nasal congestion, eyelid oedema and ptosis. The syndromes vary in the duration and frequency of the attacks, with cluster headache (CH) attacks being the longest and least frequent, through paroxysmal hemicrania (PH), to the Short-lasting Unilateral Neuralgiform headache attacks, with the most frequent and shortest attacks. Hemicrania Continua has recently been included in the classification of TACs, although it shares characteristics of both migraine and the TACs.

Cluster headache

This is the commonest of the TACs, with an incidence of around 0.1%. There is a male: female predominance of 3:1. Attacks of severe to excruciating pain occur in and around the eye, retro-orbital region, and side of the head. Attacks last 15-180 minutes, and can occur once every other day, up to eight times per day.[1] The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis end/or eyelid oedema, forehead and facial flushing, a sense of fullness in the ear, and/or with restlessness and agitation.

Characteristically the pain can wake the patient from sleep at night, often at a set time (such as 90 minutes after falling asleep). Attacks can be triggered by strong smells such as paints, perfumes or petrol fumes, and by ingestion of alcohol – which will typically induce an attack within a few minutes, as opposed to migraine attacks which are induced within hours of ingesting alcohol.

Episodic and Chronic Cluster Headache

In 85-90% of cases, CH occurs as Episodic Cluster Headache (ECH), in bouts (or 'clusters'), lasting weeks or months at a time, separated by remission periods of months or years. Patients with attacks for more than a year's duration without a remission of a month have Chronic Cluster Headache (CCH). CCH can arise de novo or can develop from ECH.

Paroxysmal Hemicrania

The attacks of Paroxysmal Hemicrania (PH) are similar to those of CH, but they are of shorter duration (2-30 minutes) and occur more frequently during the day (at least five attacks per day for more than half the time). The ipsilateral autonomic features are similar to CH. A diagnostic criterion of PH is that the attacks are abolished by Indomethacin.

Attacks can wake the patient from sleep, although much less frequently than in CH;[2] and there is less circadian and annual periodicity than in CH. Triggers to attacks included stress, relief from stress, and exercise (as with triggers to migraine), and also alcohol and neck movement.[2] As in CH, PH can occur as episodic or chronic forms, although CPH is commoner than EPH.

Short-lasting Unilateral Neuralgiform headache attacks (SUNCT and SUNA)

These syndromes have attacks of the shortest duration (1-600 seconds) and most frequent (up to hundreds of times per day). Originally known as SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing), it became apparent that any one or all of the full range of autonomic features could be present ipsilateral to the side of the attack; and therefore the ICHD-3 beta classification distinguishes between SUNCT and SUNA (Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms), where either conjunctival injection, or tearing, or neither, but not both, are present.[1]

Again, SUNCT/SUNA can occur as either episodic or chronic forms (the latter is more common). There is a slight male preponderance in SUNCT. Multiple cutaneous stimuli have been reported to trigger attacks of SUNCT/SUNA, including:[3]

- Touching the face or scalp
- Bathing or showering
- Washing or brushing hair
- Shaving
- Nose blowing
- Chewing or eating
- Brushing teeth
- Talking
- Coughing
- Exercise
- Light (including sunlight and fluorescent lights)

Attacks can be of three types: single stab attacks; groups of stabs; or a saw-tooth pattern, with a group of stabs occurring in quick succession such that the pain does not return to baseline between stabs. The sawtooth attacks, made up of

Table 1: Differential Diagnoses of the TACs

Headache Syndrome	Differential Diagnoses	Distinguishing Features
CH	Migraine with prominent autonomic features	Agitation usually present in CH; also circadian and circannual periodicity
PH	CH	PH responds absolutely to indomethacin
SUNCT/SUNA	1)Trigeminal Neuralgia (TN)	Autonomic features and agitation are more prominent in SUNCT/SUNA, plus no refractory period between attacks as in TN
	2) CH or PH (groups of stabs of SUNCT/SUNA)	Cutaneous triggering more common in SUNCT/SUNA; also characterisation of the attack- stab/group of stabs/sawtooth
HC	1)CH with background pain 2)migraine with chronic background pain	HC responds absolutely to indomethacin

many single attacks of SUNCT/SUNA, can endure for minutes or hours, and can often be mistaken for longer-lasting TACs.[3] Figure 1 depicts the three different types of attacks of SUNCT/SUNA.

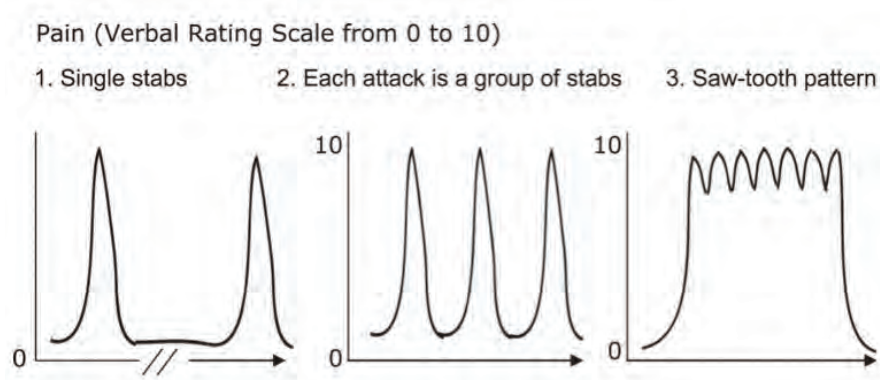

Figure 1. The different types of attacks in SUNCT/SUNA. Reproduced with permission from OUP 2006 (Cohen A S et al. Brain 2006;129:2746-2760).

Hemicrania Continua

Hemicrania Continua (HC) is a syndrome of continuous unilateral head or facial pain, without a moment's break, for at least three months' duration. There is a background constant pain with exacerbations up to moderate or severe intensity that can last for hours or days. The exacerbations are associated with ipsilateral cranial autonomic symptoms, as in the other TACs, and also agitation or restlessness. The symptom of itching or grittiness in the eye has been often cited as an identifying feature of HC, but a recent case series suggested that it was in fact another autonomic symptom referable to all the TACs.[4] However HC also shares some features of migraine, with some patients reporting aggravation of the pain by movement. Migrainous symptoms such as photophobia and phonophobia can be seen in all the TACs,[5] but are more common in HC.

Hemicrania continua is usually unremitting, but can occur in the remitting subtype where there are pain free periods lasting at least a day without treatment.

Differential diagnosis of the TACs

Table 1 outlines the differential diagnoses of the TACs, and suggests some clinical points to differentiate between them.

Symptomatic TACs secondary to structural lesions

The TACs are generally thought of as primary headache disorders. However there are an increasing number of reports of TAC mimics due to posterior fossa or pituitary lesions. In particular, SUNCT and SUNA are disproportionally over-represented in headaches due to pituitary micro- or macroadenomata.[3,6]

Pathophysiology of the TACs

Functional imaging studies have shown activation of the region of the posterior hypothalamus in CH,[7] SUNCT[8] and PH.[9] As recently reviewed in ACNR, the areas involved in migraine are the dorsal pons, locus ceruleus and periaqueductal grey matter.[10] Interestingly, HC, which shares clinical features of both migraine and TACs, has activation in both hypothalamus and brainstem structures.[11]

A striking feature of the TACs is the autonomic component accompanying each attack of pain. This is mediated by the trigeminal autonomic reflex, where stimulation of trigeminal efferents can result in cranial autonomic outflow.[12] Thus, some degree of autonomic symptomatology is a normal physiological response to cranial and facial pain, and can be present in other headache syndromes such as migraine, especially in the paediatric population.[13]

However in the TACs the autonomic symptoms are more prominent, in addition to agitation during an attack (especially in CH and SUNCT), which suggest a common pathophysiological link. It is suggested that a central disinhibition of the trigeminal-autonomic reflex, as well as hypothalamic direct modulation of the trigeminovascular nociceptive pathways, are responsible. Experimental results suggest that stimulation of the posterior hypothalamus significantly inhibited light and facial-skin evoked activity of neurons in the trigeminal caudalis and upper cervical regions,[14] which further imply the role of the hypothalamus in trigeminal pain syndromes.

Epidemiology of the TACs

Although rare disorders, the TACs and CH specifically may have a genetic preponderance. Genetic epidemiological surveys have shown that first-degree relatives of CH patients are more likely to have CH than in the general population.[15] The HCRTR2 1246G > A and the ADH4 925A > G polymorphisms have been associated with CH. Pharmacogenetic studies have suggested that the GNB3 825C > T polymorphism may modify treatment response to triptans among CH patients by altering the signal transduction cascade via G protein-coupled receptors.[16]

Treatment of the TACs

CH is the only TAC for which an acute (abortive) therapy is indicated to treat an individual attack. The other TACs are too short and too frequent for abortive therapy to be of any practical use, and therefore the mainstay of treatment is preventive therapy. Short-term preventive therapies are useful in CH and SUNCT, in order to allow a pain-free window for titration of preventive medications.

Cluster headache

Abortive therapies in CH include Sumatriptan 6mg to be given subcutaneously at the start of the attack, and this should abort an attack within a few minutes. This can be taken a maximum of twice a day. An alternative is Sumatriptan 20mg intranasal spray, which can be taken a maximum of three times a day.

Oxygen in high dose and high flow (12L/min for 15 mins) taken at the start of the

Table 2. Treatment Options for TACs

	CH	PH	SUNCT/SUNA	HC
Abortive therapies	Oxygen Sumatriptan sc Sumatriptan in	—	—	—
Short-term preventive	Prednisolone	—	Intravenous lidocaine	—
Preventive therapies				
Indomethacin	—	+++	—	+++
Verapamil	+++	+	—	+/-
Other calcium channel antagonists	—	+	—	—
Topiramate	++	+	+	+
Lithium	++	—	—	—
Lamotrigine	—	—	+++	—
Gabapentin	—	—	++	+
Amitriptyline	—	—	—	+
Non-pharmacological				
GON blockade	++	+/-	++	++
ONS	++	+	++	++

attack has been proven effective in a recent placebo-controlled trial.[17]

Preventive medications for CH are outlined in Table 2. In Episodic CH the preventive medications should be taken only during the bout, and are of no benefit if taken during the remission period. For patients with short bouts (six weeks or less) then verapamil is of less practical use, as the dose may only be titrated up every two weeks, thus taking a longer time to achieve a therapeutic dose.

Verapamil should be started at 80mg tds, and increased every two weeks by 80mg, to a maximum of 960mg tds, or at whichever dose supresses the attacks, or until side effects intervene. An ECG should be performed prior to commencement of verapamil, and also at every two weeks prior to each dose increase, in order to prevent the side effect of first degree heart block.[18]

In terms of short-term preventive therapy, intravenous methylprednisolone has been used as a short-term regimen in order to induce clinical remission,[19] and thus allow the upward titration of preventive medications during the pain-free period. Oral prednisolone at doses of 40mg daily or higher, have for many years been known to effect a short-term remission in CH.[20] Current practice is to give 60mg/day for three days, then to reduce by 10mg every three days, to zero.

Paroxysmal Hemicrania and Hemicrania Continua

Indomethacin is the gold standard treatment for these conditions, and in fact can be used as a diagnostic tool in the form of the modified Indotest.[21] Oral doses start at 25mg tds, increasing to 50mg tds, and subsequently to 75mg tds in partial or non-responders. If there is no response after 10 days at the highest dose, then the diagnosis of PH should be reconsidered.

If indomethacin is not tolerated, or in a subset of patients for whom indomethacin is not entirely beneficial, then a second line option would be an alternative NSAID or a COX II inhibitor such as rofecoxib or celecoxib, although with the caveats of the known side effects of these drugs. Topiramate has been reported of benefit, as has verapamil or other calcium channel antagonists such as flunarizine and nicardipine.

SUNCT/SUNA

Intravenous lidocaine, infused at 1.5-3.5 mg/kg/hour, for up to a period of seven days, has been shown to be benefical in case series, and is useful for patients with severe exacerbations, also with severe cutaneous triggering that render them unable to eat or drink. The beneficial effect of the lidocaine can last for weeks or even months after cessation of the infusion, and is therefore useful as an interim measure in order to titrate up the dose of oral medications.[21]

In terms of oral agents, lamotrigine has been reported as benefical in a number of case series, as has gabapentin. Topiramate may also be useful.

Hemicrania Continua

As in PH, the gold standard of treatment in HC is indomethacin. If indomethacin is poorly tolerated, options include other NSAIDS, COX-2 inhibitors, and topiramate. There are small series showing benefit in 66% of patients with amitriptyline, 20% on gabapentin, and 10% on topiramate.[22]

Non-pharmacological treatments

Greater Occipital Nerve (GON) injection

Nociception in the head and face, from the trigeminal and upper cervical afferents, converge at the trigeminocervical complex. Modulation of this system, either by blockade or stimulation, can abolish or reduce pain on the ipsilateral side. Injection of a local anaesthetic and/or steroid into the region of the greater occipital nerve has proven beneficial in many headache syndromes, including migraine, CH, HC, and new daily persistent headache.[23] The evidence for PH is less clear, and comes from single case reports. There is a case series for patients with SUNCT and SUNA who responded well to injections of 2% lidocaine and 80mg depomedrone, with pain-free times ranging from one week to six months.[8]

Occipital Nerve Stimulation

Occipital nerve stimulation (ONS) has been employed to good effect in patients with SUNCT[24] CH[25] and HC.[26] Again the evidence for ONS in PH is limited.

Other sites for stimulation in CH include the hypothalamus and sphenopalatine ganglion; the latter being the only one to have an acute abortive effect.[27]

Hypothalamic Deep Brain Stimulation (DBS)

As the region of the posterior hypothalamus is implicated in the pathophysiology of the TACs, there have been case series of deep brain stimulation to the region of the posterior hypothalamus with some success in CH and SUNCT, and a single case report in PH.[28] However the European Headache Foundation has suggested that these procedures should only be used in patients with medically intractable syndromes from tertiary headache centres, either as part of a valid study, or which have shown to be effective in such controlled studies with an acceptable side effect profile.

Summary

The TACs include Cluster Headache, Paroxysmal Hemicrania, Short lasting Unilateral Neuralgiform Headache attacks, and recently including Hemicrania Continua. The syndromes vary according to the severity and duration of the attacks (aside from HC which by definition is a continuous

headache). The pathophysiology is suspected to involve the region of the posterior hypothalamus, which by direct hypothalamic-trigeminal connections, and by modulating the trigeminal-autonomic reflex, can result in pain and ipsilateral autonomic symptoms. Medical treatments are specific to each syndrome, apart from greater occipital blockade or stimulation, which may be beneficial in most of the TACs. ◆

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Regenerative Drugs for Parkinson's Disease

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Summary

- No drug yet has convincing data to prove that it has neuroprotective properties in PD.
- Many agents show promise in the laboratory and are undergoing Phase 2 evaluation of clinical efficacy.
- Repositioning of agents already licensed for use in man avoids major safety and tolerability concerns.
- The existence of a wide range of agents, with diverse mechanisms all related to our latest understanding of PD neuro-degeneration, provides hope that one or more of these may translate to a clinically useful therapy.

While neuro-"regeneration" is conceptually distinct from neuro-protection, from the perspective of therapeutic development in Parkinson's disease, progress indicating any effect in slowing, stopping or reversing neurodegeneration would be warmly welcomed. Any mechanism through which an agent may protect against neuronal degeneration, might similarly allow endogenous repair processes to resume, therefore there is no attempt to distinguish between these concepts here.

There have been several major disappointments in this field in recent years. Creatine, Coenzyme Q10 and Cogane all showed promise as potential disease modifying agents in PD but all failed when formally evaluated in large phase 2 trials. Our enthusiasm for the next generation of candidates must thus be tempered by these disappointments and necessitates closer scrutiny of the evidence supporting potential efficacy before the major financial investment is made to embark on further very expensive, large scale trials. The agents that are currently at various stages in the "PD regenerative pipeline" include;

Isradipine

Some large epidemiological studies have suggested a slightly lower risk of PD among individuals treated with brain penetrating dihydropyridine calcium antagonists such as isradipine.[1] However similar benefits are associated with the non-brain penetrating amlodipine, and this association has been questioned as simply reflecting that patients prescribed these drugs are exposed to a specific pattern of health care, a behaviour which has greater relevance for PD risk then the exposure to the agent itself.[2] However credence is given from laboratory work showing that nigrostriatal cells have calcium dependent pacemaking activity which is highly energy demanding that can be blocked by this class of drugs.[3] Furthermore, in mouse models of PD, isradipine protects against dopaminergic cell death from either the MPTP or 6-hydroxy dopamine mitochondrial toxins.[4] There are, as yet, no data regarding the efficacy of this drug in transgenic animals or animals exposed to alpha synuclein preformed fibrils, currently considered to represent closer models of the neurodegenerative process of PD.[5]

Thus far, the clinical trial data in patients with PD shows that the 10mg dose of the drug is well enough tolerated with respect to blood pressure lowering, although the evidence of beneficial effects (~1 point advantage in the total Unified Parkinson's disease rating scale (UPDRS) score after one year) is modest and did not reach statistical significance.[6] Whether this effect size is of clinical importance is debatable, however these data have already been considered sufficiently strong to secure $23m funding from NIH to take this agent to a phase 3 trial.

Inosine

Epidemiological studies also suggest that higher levels of plasma uric acid are associated with a slower rate of progression of PD.[7,8] Again, while intriguing, this does not confirm that this association is in any way causal; perhaps individuals with higher CNS dopamine levels gain greater (dopamine-mediated) pleasure from uric acid rich foods/wines. Nevertheless, there are also some supportive data from the study of in-vivo animal models of PD that uric acid may have neuroprotective properties.[9] Uric acid itself is rapidly metabolised in the gut however oral administration of inosine, the precursor to uric acid, can successfully increase plasma and CSF uric acid levels.[10]

In a pilot clinical trial, patients with low levels of serum urate at baseline were recruited and randomised to receive low or medium doses of inosine or placebo for two years.[11] Most participants continued with their allocated drug for six months, however the number of participants had fallen by 50% at one year and only a small minority were still exposed to inosine/placebo beyond one year, although there appeared to be only a small risk of causing gout or kidney stones. Overall, the difference in the rate of worsening based on change in total UPDRS score per year indicated only a very slight advantage (~1 point) in the higher dose inosine treated group only, and careful consideration must be taken to decide whether this magnitude of signal of effect justifies the major further investment currently being sought.

Intra-putaminal Glial cell derived neurotrophic factor (GDNF)

In 2003, an open label trial of intra-putaminal GDNF infusion in PD patients reported positive clinical and radiological outcomes, however a subsequent double blind trial could not replicate these beneficial effects.[12,13] Prolonged

Agent	Putative mechanism of action	Already licensed for use in humans?	Neuroprotective in vivo models?	Stage of human trial development
Isradipine	Calcium channel antagonism	Yes	Protects against MPTP and 6-OH dopamine toxicity in mice	Published phase 2 data. Due to start Phase III
Inosine	Anti-oxidant	Yes	Protects against 6-OH dopamine in rats	Published phase 2 data. Applying for funding for Phase 3.
Intra-putaminal GDNF	Neurotrophic factor	No	Protects against MPTP toxicity in non human primates	Phase 2 trial in progress
GM1 ganglioside	Neurotrophic factor	No	Protects against MPTP toxicity in non human primates	Published delayed start Phase 2 data
Deferiprone	Anti-oxidant	Yes	Protects against MPTP in mice	Published delayed start Phase 2 data.
Exenatide	GLP1 agonist	Yes	Protects against MPTP, 6-OH, LPS dopamine in mice	Published open label data. Due to start double blind phase 2.
Pioglitazone	Anti-inflammatory	Yes	Protects against MPTP toxicity in non human primates	Double blind phase 2 in progress
Alpha synuclein vaccination	Reduction of alpha synuclein levels	No	Reduces neurodegeneration in alpha synuclein transgenic mice	Safety studies in set up
Ambroxol	Increases GCase transcription & increases lysosomal biogenesis	Yes	In vitro data from human fibroblasts only.	Pharmacokinetic studies in set up.

debate followed regarding differences in the methods used to administer the GDNF in the double blind trial that may have explained this discrepancy. However further concerns emerged regarding the significance of a) anti-GDNF antibodies and b) cerebellar toxicity, observed in some laboratory animals treated with prolonged GDNF infusion.[14] Enthusiasm has been further dampened by the subsequent lack of beneficial effect of Cogane, an orally active GDNF inducer, and neurturin – a GDNF analogue delivered via gene therapy vector.[15,16]

Nevertheless, inspired by the original results and long term follow up of patients in the open label trial, the team in Bristol, UK are recruiting further patients to a further double blind trial to revisit and clarify the potential of intra-putaminal administration of GDNF.

GM1 ganglioside

GM1 ganglioside is an important component of neuronal membrane signalling and has been shown to have neuroprotective effects in the toxin based animal models of PD.[17,18] In a double blind delayed start designed trial, early use of GM1 (administered as iv loading injection followed by twice daily subcutaneous injection) had clear acute symptomatic effects (~5 point improvement on the motor subsection of the UPDRS).[19] Individuals allocated to receive GM1 after a 24 week delay also had comparable symptomatic improvement but did not catch up with the benefits seen in the early start group during the two year exposure period. After cessation of the drug, all patients slowly deteriorated but again those individuals treated earlier had a modest advantage at all subsequent time points over the next two years. There is therefore ongoing interest in the potential of GM1 as both a symptomatic as well as a potential neuroprotective drug in PD.

Deferiprone

Excessive levels of iron have been identified in the substantia nigra of PD patients correlating with disease severity.[20] Deferiprone is a licensed treatment for iron chelation, known to cross the blood brain barrier.[21] In a further delayed start design trial, deferiprone reduced levels of iron in the SN seen using T2* MRI, associated with a two point improvement in the UPDRS motor subscore.[22] This effect size is clinically important although these data cannot yet be interpreted as neuroprotection given that it remains possible that there is some interaction between iron chelation and dopaminergic treatment. A further pilot trial is ongoing. (Clinical trials.gov NCT01539837).

Exenatide

Exenatide is an agonist for the Glucagon-like peptide 1 receptor (GLP-1), the stimulation of which leads to an increase in insulin release and proliferation of pancreatic beta islet cells.[23] It is licensed for the treatment of type 2 diabetes mellitus. In vitro studies have suggested additional neurotrophic actions and in vivo studies have shown neuroprotective effects on dopaminergic cells in the toxin based animal models of PD.[24,25,26,27] Exenatide has also been shown to have beneficial effects on noradrenergic and serotonergic systems with positive behavioural effects in animals indicating potential relevance for non-motor symptoms of PD such as memory and mood disturbance.[28,29]

In a small open label trial, administration of exenatide by twice daily subcutaneous injection for 12 months was accompanied by a five point advantage on the motor subsection of the UPDRS together with a similar improvement in cognitive performance.[30,31] These advantages persisted 12 months after cessation of exenatide, however given the open label trial design, these results must be interpreted with caution unless/until they are replicated in a double blind trial.

Pioglitazone

Pioglitazone is a licensed treatment for type 2 diabetes mellitus, and acts to improve insulin resistance via an action on the peroxisome proliferator activated receptor gamma (PPARγ) receptor. In the laboratory it has been shown that this agent reduces the expression of pro inflammatory cytokines by reactive microglia.[32] In the non-human primate MPTP model of PD, pioglitazone was found to reduce the loss of dopaminergic neurons and preserve motor function.[33]

As a result of these observations, a phase 2 trial of pioglitazone in 216 patients with PD is underway but as yet there are no efficacy data in humans with PD. However, despite the robust laboratory data supporting study of pioglitazone in tandem with intriguing mechanistic links between pioglitazone, mitochondrial function and PD, a potential association between pioglitazone and a small increased risk of bladder cancer has recently been discovered; in a meta-analysis it was calculated that this amounted to approximately five cases of bladder cancer for every 100,000 person years of pioglitazone treatment[34] Careful scrutiny of clinical trial data regarding any benefit on PD progression will be required before any conclusion can be drawn in evaluating the acceptability of this level of risk.

Alpha synuclein vaccination

Given that we know that excessive levels of (even normal) alpha synuclein are sufficient to cause PD, the concept of using vaccination has arisen, to try and lower these levels.[35] The major problem has been identifying whether and how a peripherally administered antibody can access the central nervous system and target a predominantly intracellular

protein, and have sufficient selectivity for alpha synuclein and no other synucleins. In a transgenic mouse over-expressing human alpha synuclein, such an antibody has been shown to successfully lower alpha synuclein aggregation in neuronal cell bodies even after peripheral administration.[36,37] This has led to the initiation of two safety trials in small numbers of either healthy individuals (Clinicaltrials.gov/NCT02095171) or patients with early PD (Clinicaltrials.gov/NCT01885494). Similar attempts are underway to try and lower beta amyloid levels as a treatment for Alzheimer's disease.

GCase stimulation

The GBA gene encodes the enzyme glucosylceramidase (GCase), and homozygous or compound heterozygous mutations in this gene are the cause of Gaucher's disease. Carrying a single GBA mutation has been shown to be the commonest genetic risk factor for PD.[38] There is a reduction in the activity of GCase in brain tissue from PD and DLB patients (with or without GBA mutations).[39] This enzyme is thus a potentially very important target for the treatment of PD. Ambroxol hydrochloride is a small molecule that protects GCase from thermal denaturation and boosts the function of GCase through upregulation of the transcription factor TFEB.[40] It is licensed for use in humans and is present in many cough syrups as it also has a role as a mucolytic. It can cross the blood brain barrier.[41] Laboratory data therefore lend strong support to taking this agent into phase 1 clinical trial in PD patients.

Interpretation

There can be some enthusiasm for the agents that currently represent the major focus as neuroprotective / neuroregenerative agents in PD. However, as yet none have emerged with robust double blind data to demonstrate a major neuroprotective effect in patients with PD.

Ongoing work to develop more useful animal models of PD neurodegeneration, and to develop a reliable biomarker that can be used to judge effects in humans with PD will be enormously helpful. Furthermore, while it is hoped that the identification of a disease modifying agent in PD will be of use in individuals with established disease, other initiatives are underway to try and identify "at-risk" populations who might be more responsive to treatments that require a relatively intact cellular architecture.

These issues and further work to understand PD pathogenesis remain of vital importance, but from a pragmatic perspective there is an urgency to efficiently confirm or exclude beneficial effects of those agents with the strongest supportive data without undue delay. To this end, there are considerable efforts to streamline and "de-risk" this process through the linked clinical trials initiative.[42] The challenges are great but with the breadth and depth of the efforts being made to overcome these challenges, it is reasonable to be optimistic. ◆

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Crash Course: Neurology, 4th Edition

This is a great book, which appears to be aimed primarily at undergraduates. It covers all the relevant areas of Neurology, explaining the structure and function, followed by insights on clinical practice. The depth is more than adequate for students, and probably for junior trainee doctors, wanting to perform well in exams.

The book is in three sections, and starts with history-taking, examination techniques and investigations (which reflects an improvement from the previous edition). The second third focuses on patients presenting with different symptoms and signs, for which the many possible differential diagnoses are outlined – a very nice way of triggering the undergraduate 'grey cells'. The largest 'third' of the book is devoted to neurological diseases and disorders. These are further sub-divided into more digestible chunks. While the sequence is laid out in the main contents pages, the same information is not provided at the beginning of each chapter – this would have improved the readability. At the end, there is a self-assessment section which is a useful add-on but would be quite insufficient to rely on as the only source of neurology practice questions prior to sitting exams.

One point which could be improved in the book is the diagrams: they consist of only three colours (which includes two shades of orange): they would probably benefit from being fully coloured.

The book is fantastic for core knowledge and clinical information, but it does not really focus on very recent or controversial facts or references. In fairness, this is probably outside the remit of a 'crash' course. The sequence of the neurological diseases chapters is rather arbitrary, but it is difficult to see how this might be improved. The style of writing is a mix between chatty and didactic, and not patronising. There is little repetition, other than providing some information in tables/boxes as an aid to memorising.

This book is definitely worth the money for undergraduates, as it covers the broad range of Neurology at a level which is sufficient for examinations and for starting out on hospital work. It is probably a benchmark in that sense. However, to focus on the structure and function of the nervous system (rather than clinical practicalities), I think the key concepts are relayed more effectively in 'Neuroanatomy: An Illustrated Colour Text (4e)' by A Crossman and D Neary. Conversely, to do some cramming of facts for undergraduate exams, I would recommend 'Rapid Neurology and Neurosurgery' by K Abhinav, R Edwards and A Whone, despite its lack of scientific detail.

Author: Mahinda Yogarajah
Series Editor: Dan Horton-Szar
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Price: £25.30

Reviewed by:
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Principles of Neural Science, Fifth Edition

The aim of this work, made clear from the outset and maintained in themes throughout the text, is to provide an understanding of the brain and its behaviour in the light of the basic neural science. Each chapter provides a scientific foundation for understanding a particular neural output or behaviour. Many chapters make use of clinical scenarios, by way of lesion studies, to complement the other experimental evidence, and these certainly add to the clinical appeal. When describing chemical transmission for example, there is an overview of the process, which leads to a discussion of the neuromuscular junction and then discussion of the central synapses and finally to description of relevant diseases, e.g. myasthenia gravis and altered reflex responses with central nervous system lesions.

To get the best out of the book requires a basic level of neuroscience knowledge. There is too much content for it to be an effective introductory text. Conversely, there is certainly enough content for it to be a valuable reference text, for the keen undergraduate or postgraduate 'student' at any level. The linking of neural science with Cognitive Psychology is especially strong, appealing to neurologists and psychiatrists with an interest in Psychology, and psychologists wishing to learn about the neural structures underpinning their discipline.

With the majority of authors based in America, the book appears to be targeted at the American medical undergraduates/ graduate students. For these readers, the scientific fundamentals may well be regarded as core curriculum. For medical students and junior doctors in the UK, pre-clinical and clinical examinations nowadays place a somewhat greater emphasis on skills than encyclopaedic knowledge. The exam-oriented UK student, of course, can find shorter and less rigorously scientific textbooks, representing a smaller investment both in terms of money and reading-time.

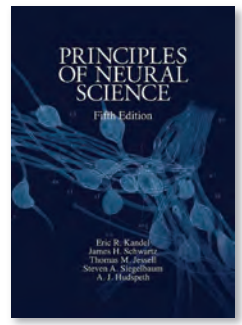
The book looks at five main areas including brain development, interaction between neural cells, neural connections giving rise to perceptions and movement, neural circuitry being modified by experience and disease processes affecting neural systems.

The book is presented in such a way that either allows the reader to fully immerse himself in a topic such as Vision, Hearing or Somatic Sensation or, alternatively, to pick a specific area of interest. There are nine 'Parts' covering such topics as Cognition and Movement; each part contains a range of chapters written by numerous authors, often further subdivided. For example, Part VI on Movement includes chapters on the vestibular system, the basal ganglia and the cerebellum. Within the latter there are sections on the signs and symptoms of cerebellar disease and cerebellar involvement in motor learning.

The highly effective illustrations range from schematic diagrams to artwork from a person with autistic traits and PET scans in patients with depression. There are also online lecturer resources, including an image bank, which complements the standard further reading suggestions.

The writing style is fluent and inviting. Many of the authors have a passion that comes across immediately, urging the reader to be fascinated. Many also include some historical background. I was captivated in particular by the opening chapter of 'The Brain and Behaviour' which gives an early map of the functional localisation in the brain, dating to the 1800s.

This book is not for clinical reference. It contains no tips to help a struggling junior doctor to manage migraine or myasthenia gravis. It would be little read on the shelf in the ward office. However, it might be very useful in the hospital library, to lend scholarly gloss to a case presentation. Far from a compendium of facts and figures, 'Principles of Neural Science' is a journey, from the nerve cell's humble beginnings to its destination in the complexities of the mind.



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Reviewed by:
Dr Dafydd Wyn Llewelyn.

Twenty years of apomorphine therapy: How does it compare to levodopa?

Highlights of a symposium held at the 18th International Congress of Parkinson's Disease and Movement Disorders, 9th June 2014, Stockholm, Sweden

Key points

- **Subcutaneous apomorphine has been an effective option for the rapid resolution of the symptoms of Parkinson's disease (PD) for over 25 years and continues to have a valuable role in PD therapy**
- **It has anti-parkinsonian efficacy comparable to orally-administered levodopa and is available for use either as an intermittent injection or a continuous infusion depending on the severity of the patient's symptoms**
- **Comparative studies in complex PD patients show apomorphine infusion has a robust motor effect resulting in a reduction in OFF periods comparable to that achieved with deep brain stimulation or intrajejunal levodopa infusion, but with a superior side effect profile**
- **Apomorphine injection is a valuable adjunctive treatment option in PD patients with morning akinesia due to a delayed onset of levodopa dose as it produces a rapid and reliable time to ON**

In 1988 the results of a pivotal clinical trial were published which demonstrated that apomorphine was the only clinically available dopamine agonist that was equipotent to oral levodopa and it was subsequently licensed for the treatment of Parkinson's disease (PD) in the UK [1]. Apomorphine now has an established role as a highly effective therapy for the management of refractory motor fluctuations in PD patients and research continues into its beneficial effects on both motor and non-motor PD symptoms. At the 18th International Congress of Parkinson's Disease and Movement Disorders held in Stockholm, Sweden, in June 2014, an international faculty, chaired by Professor Andrew Lees (London, UK), convened to review the extensive clinical experience with subcutaneous apomorphine over this time and to examine why it continues to have an important role in PD therapy.

In PD patients with complex or advanced disease who have severe motor complications, such as end-of-dose wearing off, unpredictable OFF or dyskinesias, refractory to optimised oral medications a choice of non-oral/transdermal therapies is available, including apomorphine continuous infusion, intrajejunal levodopa continuous infusion (IJLI) and bilateral stimulation of the subthalamic nucleus (STN-DBS). Professor K. Ray Chaudhuri (London, UK), provided an overview of the available data directly comparing apomorphine infusion with placebo, conventional therapy, and the alternative options for advanced disease. When compared to optimised conventional (oral or transdermal) therapy, he noted that apomorphine infusion has been shown to produce significant improvements in UPDRS motor scores, quality of life measures and non-motor symptoms (NMS) [2]. The beneficial non-motor effects include improvements in sleep and urinary function and notably there are no negative effects on hallucinations or cognition [2].

Apomorphine infusion and IJLI have been compared in a large-scale, real life, multicentre, European study, EuroInf [3]. Results have confirmed that both treatments have equivalent, significant benefits on UPDRS motor scores and provide similar improvements in health-related quality of life measures, however the side effect profile observedwith apomorphine is superior. When compared to STN-DBS, the limited data suggest that while both treatments result in significant clinical improvements in complex PD symptoms, STN-DBS provides greater benefits in dyskinesia reduction [4, 5]. However, unlike apomorphine, STN-DBS is associated with worsening cognitive and neuropsychological outcomes which needs to be considered when selecting therapy for certain PD patients.

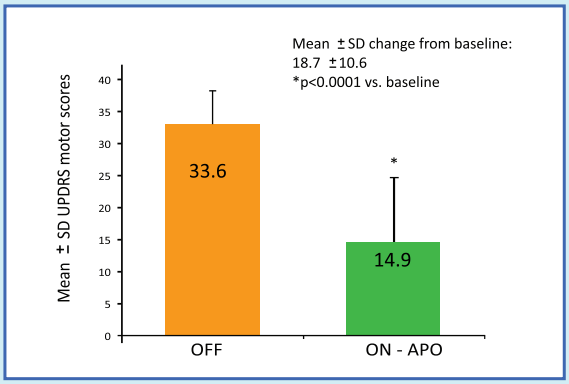

Figure 1: Change in mean UPDRS OFF motor score after an apomorphine injection dose

Professor Stuart Isaacson (Florida, USA) discussed the role of apomorphine injection in PD management. He noted that as their disease progresses many PD patients experience OFF periods despite optimised oral therapy, often requiring multiple medications. These OFF periods are due to a combination of end-of-dose wearing OFF and delayed time to ON (TTO) which can result from delayed gastric emptying (gastroparesis), a common symptom in PD patients. In gastroparesis, the levodopa dose is delayed reaching its site of absorption in the small intestine limiting its clinical effect. Non-oral formulations that avoid the gastrointestinal route offer an alternative option to relieve motor fluctuations in this setting. Interim results from AM IMPAKT (Apokyn for Motor IMProvement of Morning Akinesia Trial) have shown that subcutaneous apomorphine injection provides effective relief to PD patients with morning akinesia due to a delayed onset of levodopa dose. Treatment resulted in a rapid and reliable TTO with 95% of patients achieving at least a 20-minute reduction in TTO with an average reduction of 40 minutes [6]. Additional benefits were also observed in the study: patients also experienced improvements in UPDRS motor score (Figure 1), Hoehn and Yahr stage suggesting possible postural improvement, and measures of quality of life. Both patients' and clinicians' assessment of the severity of illness relative to akinesia and motor function showed it to be improved.

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Prescribing information can be found on the adjacent page

This article was commissioned by Britannia Pharmaceuticals Ltd and was written by Helen Lawn & Associates. The Britannia-sponsored symposium was held on 9th June 2014 during the recent 18th International Congress of Parkinson's Disease and Movement Disorders in Stockholm, Sweden

APO2-0814-0503 Date of preparation: August 2014

Rapid reliable 'on' for Parkinson's disease

APO-go PEN provides rapid and reliable 'on' **for patients with morning akinesia**, reducing time to on by an average of 40 minutes[1]

APO-go® Apomorphine hydrochloride
PRESCRIBING INFORMATION Consult Summary of Product Characteristics before prescribing. **Uses** Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication **Dosage and Administration** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly. and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and broncospasm. **Side Effects** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects* **Presentation and Basic NHS Cost** APO-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers**: APO-go Ampoules: PL 06831/0245 APO-go Pens: PL 06831/0246 APO-go Pre filled syringes: PL 06831/0247 **Legal Category** POM **Date of last revision**: March 2014 For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK

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1. AM IMPAKT Study interim results. Presented at International Parkinson and Movement Disorder Society. Treatment of Parkinson's Disease: Past, Present and Future. March 2014, Miami, Florida, USA.

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The Shape of Training:

what is it and how does it affect Neurology?

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Introduction

'Shape of Training: Securing the future of excellent patient care' is the report of an independent review, led by economist Professor David Greenaway, into medical training in the UK and was published in October 2013. The stated aims of the Shape of Training (SoT) Review were to "make sure we continue to train effective doctors who are fit to practise in the UK, provide high quality care and meet the needs of the patients and the public". It also aimed to ensure that UK trained doctors are competent to deal with changes in the demographics of society; managing patients with chronic illness and multiple co-morbidities. The Shape of Training Report recommends a change to postgraduate medical education and training to create a better balance between doctors able to provide general care in a specialty area as well as those providing a more specialised service. The review was co-sponsored by Health Education England, the Academy of Medical Royal Colleges, the General Medical Council, the Medical Schools Council, Conference of Postgraduate Medical Deans of the UK, NHS Education Scotland and representatives from Northern Ireland and Wales.

Background

In recent years, significant changes have been made to UK medical training, based on recommendations from a number of seminal reports. In 2007, the Tooke inquiry reported on the controversial Modernising Medical Careers (MMC)[1] programme and called for an overhaul of medical training with an emphasis on a more flexible and broad-based approach. Several other reports have been published describing deficits in standards of UK healthcare that have highlighted the need to re-examine training in addition to service organisation and workforce planning.[2-8] The central theme that has emerged from these reports is that healthcare is becoming increasingly disjointed; expert specialist services exist but a lack of collaboration means that patients with complex medical needs are often being failed. Furthermore, acute and internal medicine is increasingly perceived as an unrewarding career choice: departments are often understaffed and medical registrars feel over-worked and under-trained.[9]

In 2013, The Future Hospital Commission (FHC) reported to the Royal College of Physicians (RCP) and proposed a new model of inpatient medical care. The proposal included a better balance between generalists and specialists in the workforce and a more collaborative approach to healthcare by ensuring that specialists retain good general medical knowledge and provide a seven-day service for patients across varied care settings.[10]

Shape of training, therefore, marks the most recent attempt to reconcile UK medical training with workforce planning for an ageing population with increasingly complex needs. The report has been met with a mixed response from doctors. The BMA and RCP have released responses to the report both of which broadly support the underlying concept of improving training proposed by SoT but raise serious concerns about shortening the length and reducing the depth of specialist training.[11,12] There is also concern that plans to rapidly implement another overhaul of training, with little trainee consultation or piloting are all too reminiscent of the MMC debacle.[13]

The Shape of Training Proposals

Here we discuss some of the proposals of SoT and how they may impact on neurology training.

1. Postgraduate training should be structured within broad specialty areas based on patient care themes

The SoT report proposes that the generalist nature of the early years of medical training should continue into the higher training. This move would address concerns that some trainees complete their training in specialties allied to medicine with suboptimal general medical knowledge or experience. However, a crucial drawback of the SoT document is its vagueness. The concept of training being centred on "patient care themes" is ill-defined. The examples of patient care themes used throughout the report are women's health, child health and mental health. It is hard to appreciate how these re-branded "themes" are any broader than their existing counterparts: obstetrics and gynaecology, paediatrics and psychiatry. By their own admission, the panel have not attempted to define how each specialty would fit into a broad-based, patient-centred training model, how patient care themes would be organised and how specialties would be grouped together.

Similarly, no attempt has been made to address specialty curricula to determine how they would be adapted to a broad-based training model, how sufficient skills and experiences would be obtained during the time available and how the curricula would be regulated. Within their training programme, it is proposed that a trainee would have the opportunity to spend up to one year working within a particular specialty. It is not clear whether this means a neurology trainee would be able to spend a year in, for example, movement disorders, or whether it means that trainees with aspirations to become neurologists would train in General Internal Medicine but get to spend one year dedicated to neurology. Any response to the

report hinges entirely on how it is interpreted and yet there is no transparent pathway laid out for consultation or implementation.

A central principle of SoT is that doctors should be trained to provide general care in broad specialties across a range of different settings. The implication of this is that SoT aims not only to alter the method of training but also to significantly alter the emerging workforce. Of the 61 medical specialties recognised by the GMC, only a handful are regarded as being true "generalists".[10] It seems that the SoT model promotes broadening training in order to create an army of generalists who can overcome current emergency department strain and understaffed medical rotas but at the expense of specialty skills. With respect to neurology, there are several reasons why this sentiment is misguided.

Firstly, the number of patients with chronic neurological conditions requiring long-term outpatient care will remain unchanged. Many of these patients will prefer to see a specialist than a generalist and there is considerable evidence that specialist care results in better patient outcomes.[14-24] Secondly, trainees who are either coerced into becoming generalists or given no certainty about whether they will be able to specialise (opportunities to specialise are proposed to be driven by local need) are likely to feel undervalued and may opt for an alternative career with more certain prospects. Finally, significantly altering the balance between numbers of generalists and specialists should be accompanied by a careful consideration of the emerging service model – the detail of which is lacking in the SoT Report.

2. Shortening of training

Both the BMA and RCP have raised concerns that the Shape of Training proposals would shorten the length of training in a way that would redefine the meaning of certification. Current postgraduate training in neurology takes at least nine years (not including research and fellowships) to achieve certification of completion of training (CCT). The model that emerges from SoT is a reduced six to eight years of "broad-based specialty training" to achieve a certificate of specialty training (CST). CST would equip doctors to "practise with no clinical supervision within multiprofessional teams and networks [and]… to make safe and competent judgements in broad specialty areas".

If neurology trainees were required to follow a general medicine training scheme with only limited opportunities to gain dedicated neurology experience, it is clear that despite being awarded a "certificate of specialty training", the emerging "specialist" would be very different from existing consultants. Existing trainees who dual-accredit in general internal medicine feel underequipped to provide general medical care on reaching consultancy and only 72% of neurology trainees feel that the existing training prepares them adequately to practise as neurology consultants.[9,25] These figures tell us that shortening training while broadening the curriculum is not a viable option.

3. Academic pathway

A positive feature of the SoT proposals is that they recognise the importance of training doctors who "straddle both clinical and academic areas" to encourage innovation and advances in medical treatments. The proposals allow for doctors moving into and out of academic training at any point during their broad-based specialty training thus encouraging a more flexible approach. They suggest that academic endeavour will no longer need to be undertaken outside of training although the detail is once again lacking.

Neurology trainees are currently facing limitations on moving out of programme to academic posts because of the perceived need to protect the clinical rotas (and therefore clinical trainees). The SoT report does not outline how these rota gaps would be filled if trainees had enhanced flexibility to move into research. Nor does the report guarantee an extension to training duration in order to allow trainees to achieve adequate clinical competence, stating only that "time spent in academic experiences will still be counted within training. It will have to be recognised that some of these doctors may occasionally take longer to reach the exit point of postgraduate training, in particular those training in craft specialties such as surgery".

4. Credentialing

Once in a consultant post, doctors would be able to gain further specialist experience via a process called "credentialing". Some existing neurology trainees already choose to undertake post-CCT fellowships to gain further subspecialty experience. Some may feel that certain subspecialty components of the existing neurology curriculum could be omitted or made optional. However, the implication of the report appears to be that a large proportion of specialty training would be acquired after certification, and would be driven by local need and finance. Many will view this as a covert means of creating a subconsultant grade, a notion that is widely unpopular with existing trainees.[26] If the majority of specialty experience were to be gained after certification, it remains to be clarified at what stage doctors would be listed on the Specialist Register. This could affect a neurologist's ability to practise overseas and for neurologists trained in other countries to be recognised as specialists here. Furthermore, it is uncertain how the specialty "credentialing" of consultants would be organised and overseen.

5. Flexibility in training

By promoting broad-based training, Professor Greenaway hoped to introduce an element of flexibility into the workforce. Trainees would be empowered to switch specialties more readily with transferable competencies. Naturally, flexibility is well-received by the workforce[11] and yet there is the subtle inference that this flexibility will favour the service providers rather than the trainees with statements such as "local workforce and patient needs should drive opportunities to train in new specialties or to credential in specific areas". Workforce planning is crucial and yet surely it cannot be imposed locally at a trainee level; should a trainee be compelled to change from neurology to respiratory medicine due to local workforce issues? The individual may well have ambitions to work elsewhere in the future. This adds to concern that the report places too much emphasis on service provision, at the cost of a considerable reduction in training duration and depth.

Shape of Training: what is the alternative?

The Shape of Training model is one proposed solution to the crisis that is facing emergency medical care in the UK. However, other proposals have been made to address the crisis that focus far more on service issues such as broadening access to high-quality specialist care, improving the attractiveness of general medicine as a career option and promoting better liaison between services and specialities.[8-10]

The Association of British Neurologists (ABN) collaborated with the RCP in 2011 to establish guidance on the shape of Neurology services for the next decade.[27] One of the three core recommendations of the ABN/RCP report was for a shift in emphasis from scheduled to emergency neurological care with consultant neurologists engaging in acute services. Neurological conditions account for more than 10% of acute medical admissions.[27] By engaging more in acute care, neurologists could considerably reduce the burden on general physicians while maintaining a specialist approach.

One of the factors contributing to understaffing of emergency care facilities in the UK is poor recruitment into careers involving general internal medicine. Negative perceptions of the medical registrar role are thought to play a major part in this shortfall. However, the idea of forcing doctors to unwillingly look after patients with general medical complaints seems fundamentally flawed. A recent report produced by the RCP has set out a strategy to improve the medical registrar role by enhancing their support system, redistributing some of their workload, improving their training conditions and raising the profile of their career.[9] To recruit trainees by offering greater incentive to those who have an interest in generalist careers rather than filling posts under duress seems a more rational and sustainable approach.

Summary

Many specialty doctors are likely to share an aspiration to improve patient services by equipping trainees with good general medical knowledge and experience and by bridging the gap between healthcare sectors whilst

incorporating a holistic approach to care. However, concerns voiced by the BMA and RCP will be upheld by many; that broadening knowledge in this way and shortening the duration of training are incompatible goals. Careful interpretation of the Shape of Training document will be crucial to avoid the covert creation of a sub-consultant grade or even the abolition of specialities as we know them. The report appears more focused around changing the shape of service than the shape of training and its "one-size fits all" approach may not be compatible with all specialties.

In responding to the Shape of Training Report, it is crucial that we separate the question of "should neurologists play a greater role in acute medicine?" from the question of whether current training is really broken. The ABNT feel that current training is fit for purpose and that as the neurologists of the future we hope to employ our specialist skills within emergency medical units to better meet the evolving needs of patients without being re-branded as generalists. ◆

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Rehabilitation in Charcot-Marie-Tooth disease type 1

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Summary

- Physical therapy and moderate exercise are positively disease-modifying in CMT1A
- Overwork weakness and fatigue need to be considered but should not prevent patients from exercising
- Continuous training at home and repeated rehabilitation measures ensure long-lasting effects
- Biomarkers will facilitate therapeutic trials as well as evidence-based rehabilitation measures

Charcot-Marie-Tooth disease is the most common inherited peripheral neuropathy with a prevalence of approximately 1 in 2,500.[1] The most common subtype is the autosomal dominant type 1A, which is caused by an intrachromosomal duplication on chromosome 17p11.2.[2,3] A consecutive primary loss of the myelin sheath leads to a secondary axonal degeneration. Characteristic clinical findings include distally pronounced muscle wasting, secondary skeletal deformities, sensory loss and reduced deep tendon reflexes.[4,5] The individual clinical phenotypes vary, even among monozygotic twins.[6] They range from subclinical manifestations to rare cases of wheelchair-bound patients. Overall, the quality of life is significantly impaired.[7]

Despite ongoing research, no curative treatments are currently available.[8] A recently published ascorbic acid trial showed no significant effect on the clinical phenotype of CMT1A patients.[9,32,36] Nevertheless, physical therapy and moderate exercises are proven to be positively disease-modifying. While a cure lies beyond the scope of physical therapy, it may prevent the rapid aggravation of the clinical phenotype.[10,11,17] Recent studies suggest that CMT patients experience physical as well as mental benefit from rehabilitation programmes, but they also perceive that the performed exercises were not specifically designed to their needs.[11] In fact there is little evidenced-based data and no common consensus on rehabilitation in patients suffering from Charcot-Marie-Tooth disease.

Rehabilitation

Overwork weakness and fatigue

The use of physical therapy in CMT used to be a controversial matter in the recent past due to the report of fatigue and overwork weakness.[12] However, a recent study examining the bilateral intrinsic hand and leg muscle strength in 271 CMT1A patients showed no difference between the dominant and the non-dominant side. This data does not support the hypothesis of overwork weakness in CMT1A and strongly argues for physical activity and rehabilitation.[13] While fatigue does exist in CMT as in other neuromuscular diseases,[14] it does not necessarily equal to muscle related fatigue, but often as a symptom of energy depletion (Ramdharry et al., 2012). Randomised, controlled studies have previously shown the positive effect of moderate exercise in CMT populations (Chetlin et al., 2004; Lindeman et al., 1995; Carter et al., 2008; El-Abassi et al., 2014). Furthermore, exercising should be encouraged, since a sedentary life-style and secondary weight gain deteriorate symptoms in CMT patients.[19]

Bracing

The characteristic pes cavus formation in patients with Charcot-Marie-Tooth disease is due to a plantar flexion deformity of the first metatarsal bone. Initially, an imbalance between the M. tibialis anterior and the peroneaus longus was thought to be the cause for foot deformity, but recent findings suggest a selective denervation on the intrinsic foot muscles as the underlying cause.[20,21] The functional strength can be enhanced by using custom-made ankle-foot orthoses (AFO). They also facilitate stretching and minimise the later development of a neuropathic Charcot joint. Yet, a prospective clinical trial revealed that the range of motion (ROM) and intrinsic strength remain unchanged.[22,23] When testing the effect of muscle strength in foot dorsal and plantar flexion the use of a dynamometry fixation device is generally recommended.[24]

Resistance training and creatine supplementation

In an observational clinical trial with 20 CMT patients, the participants received resistance training either with or without additional creatine monohydrate supplementation. After an initial baseline assessment, patients underwent 12 weeks of, mainly home-based, resistance training (3 session/week). The exercises were performed with adjustable wrist and ankle weights, according to the individual baseline strength. Special focus was given to knee extensors / flexors and elbow extensors / flexors exercises. The intensity of training was systematically increased in terms of weight and number of repetitions. Patients tolerated this moderate exercise well and showed high compliance. The training sessions significantly improved the activity of daily life (ADL) and strength. However, no differences in performance were observed when comparing patients with or without creatine monohydrate supplementation.[16] A follow-up study 20-34 months after completion of resistance training showed that patients who

continued as well as patients who discontinued their training, lost strength in comparison to their baseline assessment. The functional abilities on the other hand, were only lost in those who discontinued their training. As a conclusion – despite inevitable loss in strength – functional gains can only be maintained by continuous exercise.[25]

TreSPE Rehabilitation programme

In a more recent pilot study, patients suffering from several types of CMT underwent a rigorous exercise regimen including treadmill, stretching, respiratory and proprioceptive exercises (TreSPE). The moderate-intensity aerobic exercises were performed twice per week for a duration of two months. After a washout of six months the baseline assessment was repeated. The assessment included a battery of outcome measures, including the MRC scale for lower limb strength, Tinetti Balance scale, Physical Performance Battery, ankle angle, oxygen consumption, complete lung function testing, peak treadmill velocity/slope, time to walk 6m and the Charcot-Marie-Tooth Neuropathy Score. In comparison to a healthy control group, no significant pulmonary differences were observed. Fatigue and overwork-weakness, that would prohibit aerobic exercises in CMT patients, did not occur. Nearly all tested parameters showed improvement after TreSPE, though mainly not statistically significant. The authors partially justify this circumstance with the small number of participants (n=8). Furthermore, they do not recommend usage of the Charcot-Marie-Tooth Neuropathy Score as well as the MRC scale for post-rehabilitation controls, since subtle improvements could not be detected with these measures. However, after 6 months of washout, most clinical measures began to deteriorate again without undercutting the baseline values. Thus, a repetition of TreSPE-training within six months is generally recommended to merely maintain clinical abilities.[10]

Quality of Life

Clinical approaches towards the improvement of the conceptual idea of 'quality of life' and mental health in CMT patients are scarce. A recently published meta-analysis of 20 clinical studies on the impairment in 'quality of life', emphasised the need for evidence-based approaches.[31] Depression, anxiety and sleeping disorders for instance, are significantly more common in CMT patients than in the general population. A holistic approach towards rehabilitation in CMT could therefore include voluntary psychological guidance, coping strategies for sensory loss and neuropathic pain, vocational rehabilitation, as well as genetic counselling.

Outlook: Biomarkers

Despite its monogenetic cause, patients with CMT1A display a marked interindividual variability of disease severity. The underlying reason for this variability is largely unknown and epigenetic factors have been discussed.[26] At present, the assessment of the individual disease severity in patients with CMT1A is performed solely by clinical and electrophysiological examinations. The CMT neuropathy score (CMTNS) is a nine item composite scale taking into account sensory and motor symptoms.[27] The CMTNS is widely applied as a primary outcome measure in clinical trials.[28] The CMTNS ranges from 0 (good clinical performance) to 36 (severely affected) and was reported to increase merely 0.68 points per year in patients suffering from CMT1A.[27] An even slower progression was reported within a recent therapy trial with ascorbic acid (0.25 points per year).[9] In light of the slow disease progression, insensitive outcome measures may increase the risk of false negative results in clinical trials. Recently, we were able to show in a large Europe-wide, clinical prospective study that certain secondary clinical outcome measures, e.g. 10m walking test, nine hole peg test and certain dynamometry measures provide valuable information on the assessment of disease severity in CMT1A-patients and could improve current scoring systems.[35] In near future biomarkers will provide powerful tools to monitor therapeutic effects.[9,29] They could also be used to quantify the effectiveness of applying physical therapy. These Biomarkers may not only serve as sensitive surrogate markers of clinical disease severity, but also identify responders to a putative therapy. CMT rats recapitulate the striking disease variability observed in patients with CMT1A. In a proof of principle study we have demonstrated that the expression levels of selected genes in sciatic nerve and skin tissue can be utilised to measure and predict the disease severity in CMT rats. Importantly, we validated these disease severity markers in skin biopsies of 46 patients with CMT1A.[30] At the moment, these markers are examined with regard to disease progression within a large pan-European consortium. In the near future we hope to provide the clinical practice with applicable biomarkers which in turn may accelerate the development of a therapy for CMT1A. Importantly, other sensitive outcome measures including skeletal muscle MRI magnetisation ratios are currently being developed.[33,34]

Summary

As no curative treatment is yet established for any type of Charcot-Marie-Tooth disease, rehabilitation and physical therapy remain the only positively disease-modifying measures to date. However, much needed evidence-based data on rehabilitation is scarce and former concerns against rehabilitation measures on the grounds of fatigue and overwork weakness can be dismissed in favour of symptom alleviating, moderate aerobic exercises. Even resistance training with light weights on ankles and wrists showed promising results. Due to the slowly progressive nature of the disease, recent studies stress the importance of continuing exercises at home, in order to maintain individual physical abilities. Randomised clinical trials with sensitive outcome measures (e.g. biomarkers) are needed to validate individual rehabilitation programmes for CMT patients. ◆

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Though much needed evidence-based data on rehabilitation is scarce, former concerns against rehabilitation measures on the grounds of fatigue and overwork weakness can be dismissed in favour of symptom alleviating, moderate aerobic exercises

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Closed Spinal Dysraphism and Tethered Cord Syndrome: A Review of Multidisciplinary Team Management

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Summary

- Embryology of spinal dysraphism
- Clinical features of tethered cord syndrome
- Multidisciplinary management of closed spinal dysraphism

Abstract

The initial diagnosis as well as the long term management of occult spinal dysraphism and tethered spinal cord is often managed by a large number of healthcare professionals including Paediatricians, GPs, Neurologists, Neurosurgeons, Rehabilitation Physicians and Therapists. We review the entity of spinal dysraphism. An approach to the evaluation and diagnosis of these entities is subsequently discussed. In addition, concepts involved in the pathophysiology, neurosurgical repair, and outcome are presented in the context of postoperative management issues that rely upon the knowledge of all professionals who may encounter these patients.

Introduction

The finding of a midline spinal anomaly in a child typically prompts referral to the Paediatric Neurosurgeon for the evaluation of an occult spinal dysraphic state. Unfortunately, occult spinal dysraphism is not always readily apparent on physical examination, but is often diagnosed retrospectively after the child presents with neurologic, urologic, and orthopaedic findings. In this article, we review the pathology and pathophysiology of occult spinal dysraphism and its relationship to the clinical entity of the tethered cord syndrome. Subsequently, concepts in the surgical and biopsychosocial management of children born with these defects will be discussed, in the context of management by the multidisciplinary team including Neurologists, GPs, Paediatric Surgeons, Physiotherapists and Neurorehabilitation Specialists.

Definitions

Spinal dysraphism is an umbrella term that describes any anomaly of the spinal cord, cauda equina or overlying tissues such as vertebrae, muscles and skin. The nervous system abnormality may or may not have associated mesenchymal or dermal changes.[1,2,3] Spinal dysraphism is essentially an anatomical term describing a spectrum of lesions and associated pathology – tethered cord is the clinical manifestation of the anatomical abnormalities that constitute spinal dysraphism. Spinal dysraphism, also called spina bifida, can be subdivided into two groups: open/aperta and closed/occulta. Closed spinal dysraphism describes lesions with intact skin that are usually incidentally discovered on radiographic or physical exam. It is characterised by a disruption in the spinous processes and laminae (mesenchymal structures) without herniation of underlying abnormal or normal neural structures through the overlying skin. However open dysraphic lesions require emergent surgical repair to prevent infection, and are comprised of a broad spectrum of abnormalities. Table 1 summarises the key features of some open and closed dysraphic defects.

The spectrum of spinal dysraphism can also be classified according to the point in spinal cord embryological development that the abnormality occurs, which will be described in the following section on embryology of spinal dysraphism and in Figure 1.

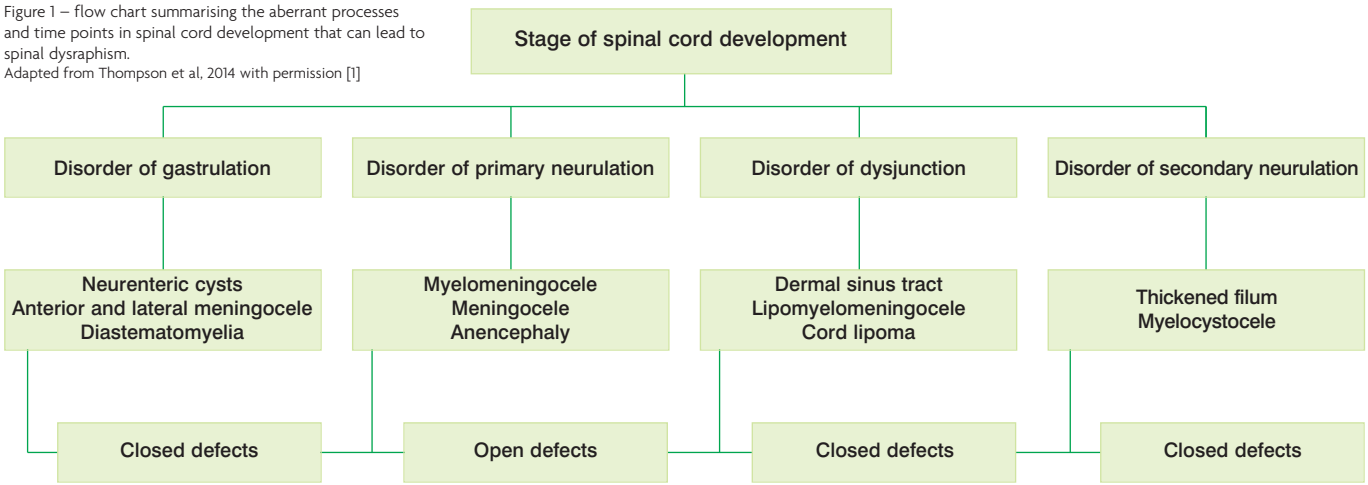
Embryology

In order to understand the mechanism by which spinal dysraphism occurs, it is important to appreciate the normal embryology of spinal cord development. This is split into three key stages and at each stage abnormalities can arise that give rise to dysraphic lesions. Essentially closed spinal dysraphism is believed to be a problem of secondary neurulation (the third stage of spinal development) whilst open dysraphism is a problem earlier on, during primary neurulation.

Table 1 – Summary of key open and closed dysraphic conditions

Open dysraphic defects	Myelomeningocele	Abnormal spinal cord exposed in the midline via defect in the posterior vertebral elements, fascia and skin
	Meningocele	Herniation of the meninges via defect in the posterior vertebral elements and fascia. but covered by skin. The cord is not involved.
	Anencephaly	Failure of anterior neuropore to close leads to herniation of a poorly developed brain – not compatible with life
	Rachischisis	Midline defect with no underlying cord. Associated with anencephaly
Open dysraphism in the majority of cases is associated with Chiari 2 malformation and hydrocephalus that may require CSF diversion		
Closed dysraphic defects	Thickened filum terminale	Filum more than 2 mm in diameter and containing abnormal tissue such as fat and fibrous bands
	Conus lipoma	Intradural lipoma attached to the distal cord
	Lipomyelomeningocele	Intradural lipoma attached to the distal spinal cord with the lipoma extending out of the spinal canal owing to a focal expansion of CSF space. Can be felt as a subcutaneous lipoma due to bony defect
	Diastematomyelia (Split Cord malformation)	Bony spur dividing the cord into two separate cords in their own dural sleeves (type 1) or one dural sac and one cord split by a fibrous band (type 2)
	Terminal myelocystocele	Expansion of the distal end of the central canal leading to an intergluteal closed cystic swelling.
	Dermal sinus tract	Epithelialised tract opens on to the skin and which may extend to the intradural space. Can have associated dermoid or epidermoid
	Neurenteric cyst	Cysts usually in the intradural extramedullary plane, lined with gastrointestinal or respiratory epithelium (endodermal origin). Can also be cranial
	Anterior and lateral meningoceles	They are very rare, and are protrusions of one or more layers of the thecal sac through a defect in the vertebrae; may be associated with Currarino's triad.

Figure 1 – flow chart summarising the aberrant processes and time points in spinal cord development that can lead to spinal dysraphism.
Adapted from Thompson et al, 2014 with permission [1]



Embryology of the normal spinal cord

Development of the normal spinal cord may be understood by viewing it as a three stage process: gastrulation, primary neurulation and secondary neurulation.

Gastrulation refers to the initial formation of a trilaminar plate that contains all three of the germ cell layers (ectoderm, mesoderm and endoderm) from which all future tissues will be derived. Ectoderm will give rise to the central nervous system and skin, endoderm to the viscera; and mesoderm to the musculoskeletal system. During gastrulation, the primitive streak of the embryo gives way to development of the midline notochord. After gastrulation which lasts from days 16 to 18 primary neurulation occurs, followed by secondary neurulation.

Essentially primary neurulation will result in the formation of the brain and spinal cord whilst secondary neurulation refers to a separate process which forms the conus medullaris and cauda equina. Primary neurulation (days 18-28) involves the development of two ectodermal folds that fuse at the anterior and posterior neuropores as well as additional midline fusion points to form the brain (rostral end) and spinal cord (caudal end). This newly formed primitive central nervous system from the process of ectodermal fusion then undergoes "dysjunction" – physical separation from the rest of the ectoderm which then goes on to become skin. After dysjunction of neural tissue from the remainder of the ectoderm that is destined to be skin, the process of secondary neurulation (essentially caudal spinal development) can begin.

During secondary neurulation from days 28-48, a separate cell pool of pluripotent stem calls located at the very tail of the embryo, termed the "caudal cell mass" gives rise to the conus, cauda equina as well as parts of the genitourinary tract and the hindgut (the viscera being endodermal). The neural structures arising from the caudal cell mass join the distal spinal cord that was created by the prior process of primary neurulation. At this point, about eight weeks of gestation, spinal tissue

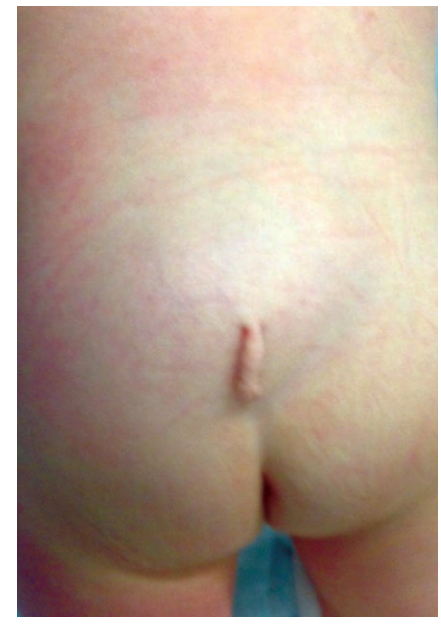


Image 1 – Photograph of a tail in a child with closed dysraphism.

extends down to the very bottom of the spinal column. The next stage is for the spinal cord to ascend rostrally in order for the conus to assume its usual position in the lumbar region. The basis of this process is by the bony vertebral column that houses the spinal cord growing disproportionately faster than the neural elements, resulting in the spinal cord being elevated proximally up the vertebral column. It is between the 8th and 18th week of gestation, that the vertebral column growth exceeds that of the spinal cord resulting in "caudal ascent" or migration of the cord to leave the thin filum terminale. By the 25th week of gestation, the growth subsides and, by two months of age the tip of the conus medullaris, the most caudal structure of the spinal cord, should be found between L1 and L2. A foetal post mortem MRI study showed that in 94.8% of cases, the conus had ascended to L3 by 40 weeks gestation.[4] Ascension stops at three months.[5,6] This process can be inhibited, however, in the presence of spinal dysraphism: the finding of the tip of the conus medullaris below the L1/2 junction can be considered pathological. A normally positioned conus does not exclude dysraphism.[7] Occult dysraphic pathologies are believed to occur from failures of secondary neural tube closure and failures at the dysjunction stage.

Epidemiology

The incidence of dysraphism is approximately 1 per 500-1 per 1000 live births.[8,9] The exact incidence of closed dysraphism is unknown but is significantly higher than that of open dysraphism, which is approximately 6 per 10,000;[10] Open dysraphism is more common in female than in male children. In open dysraphism, women with a history of a previous pregnancy complicated by dysraphism carry a 3 to 5% risk of recurrent spinal dysraphism.[11,12] The prevalence of all types of dysraphism that could be diagnosed at birth in the United States decreased almost a quarter between 1995-1996 and 2003-2004 following food fortification with folic acid.[13]

Both genetic and environmental factors have been implicated in the aetiology of spinal dysraphism. A number of genes have been investigated and no single causative gene has been identified, although genetic pathways in folate and 1-carbon metabolism are believed to be important.[14] Environmental factors which have been demonstrated to be associated with high dysraphism risk are folate deficiency, use of some anti-epileptics, poor socio-economic status, maternal age greater than 40 or less than 19.[15] Geographical variations in the prevalence of dysraphism have been reported in first and third world settings, although no firm conclusions regarding ethnicity being a risk factor have been reached.

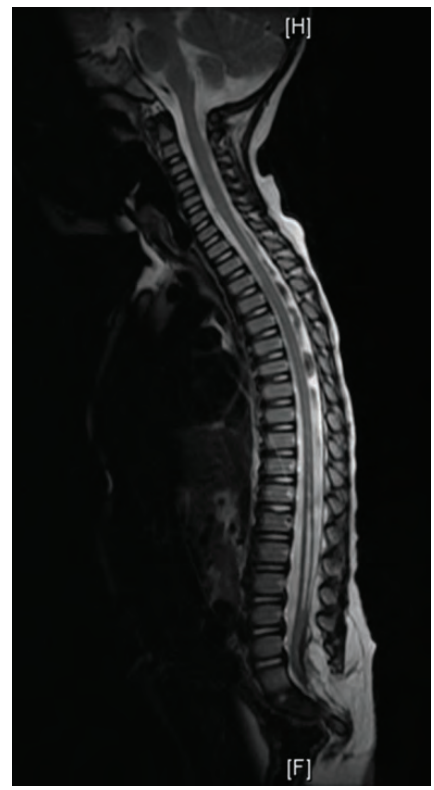
The socioeconomic burden of dysraphism was investigated in a recent meta-analysis of 14 cost of illness studies which showed that key costs were hospital stay, long term complications of dysraphism throughout adulthood and caregiver costs.[16]

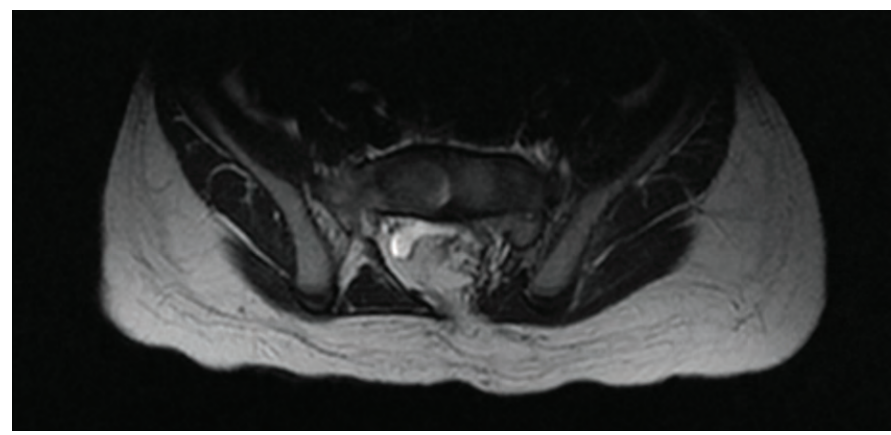
Known genetic syndromes associated with NTDs are trisomies 13 and 18 and Currarino triad[17] and up to 10% of spina bifida cases are associated with chromosomal defects.[18]

Diagnosis and presentation

Open dysraphism is diagnosed by antenatal ultrasound and foetal MRI. The 2008 NICE guidelines on antenatal care recommend that when routine ultrasound screening is performed to detect spina bifida, it is not necessary to perform alpha-fetoprotein levels.[19] The imaging is also useful to identify associated disorders such as hydrocephalus. Occult dysraphism is not usually identified antenatally. It is detected either when a midline cutaneous marker prompts further investigations or when the patient has an MRI for clinical suspicion of tethered cord or for other indications. Approximately 6% of closed dysraphism is associated with Chiari 1 malformation.[20] It is therefore important to evaluate children with occult dysraphism for hydrocephalus and syringomyelia related to a Chiari 1.

Image 2A (top) and 2B (bottom): sagittal and axial T2 MRI scans of a child with lumbar lipomyelocele. There is posterior sacral agenesis. The spinal cord is low lying with the conus lying at S1. The large intradural lipomatous extension reaches L4 level superiorly, and herniates through the posterior sacral defect. There is dilation of the central spinal canal from T9 - L4, which is at its widest calibre at L2/3. The cervical and upper thoracic spinal cord are normal.





Introduction to Tethered Cord Syndrome (TCS)

Tethered cord is essentially a clinical diagnosis. It refers to patients with dysraphic anomalies who have manifested clinical features of neurological, urological and orthopaedic pathology secondary to the dysraphism. The clinical heterogeneity of tethered cord syndrome makes the diagnosis a challenge. It may present at birth or be asymptomatic only to progress with growth and may present for the first time in adulthood.[21] Finally, it may present as new or progressive signs in a patient with a known dysraphic state. The physical findings of occult spinal dysraphism do not necessarily correlate with the development of clinical tethered cord syndrome. Tethered cord syndrome is characterised by the progressive development of sensorimotor neurological dysfunction, sphincter and sexual dysfunction, and orthopaedic symptoms. These signs and symptoms often follow a period of growth, i.e. school age children between 5 and 15 years of age, and are the most common presentation.

Hypotheses for the pathophysiology of TCS

The terminology "tethered cord" refers to the fact that the cord or conus is low lying and was thought to have traction placed on it as the vertebral column grows whilst the nerve roots of the cauda equina are still adherent to the lumbosacral area and cannot ascend in parallel to the growing vertebral column. Nerve root stretch is theorised to result in vascular compromise with a decrease in blood flow and mitochondrial activity and metabolic derangement on the background of structurally abnormal neural tissue.[22,23,24] Fibrous and fatty bands were identified in a histopathological and imaging study of dysraphism[25] and these may cause mechanical "tethering". These

hypotheses have been debated in the literature, but the pathophysiology of the tethered cord syndrome remains unclear.

Cutaneous manifestations of the tethered cord syndrome

The main cutaneous stigmata of tethered cord are hairy patches, dermal sinuses, hemangiomas, subcutaneous lipomas, atretic meningoceles, abnormal dimples and skin tags.

Approximately half of clinically suspicious midline spinal cutaneous lesions are associated with dysraphic pathology.[26] Approximately one third of patients with dysraphism show some cutaneous lesion.[27] Skin manifestations are often single but less commonly can be multiple.

One lesion of spinal dysraphism is hypertrichosis, or the "hairy patch". This lesion is described as a midline often V-shaped patch of excessive hair in the newborn, not a collection of sparse hair. Hairy patches associated with occult dysraphism are usually well defined and localised as opposed to hirsutism. Hairy patches can be associated with underlying split cord malformation.[1]

The finding of a lipoma, or a subcutaneous fat pad, is the most common marker that signifies underlying spinal dysraphism.[28] In addition, 80-90% of spinal lipomas have an additional cutaneous lesion.[29] The lipoma may be limited to the dermis, may extend into the intraspinal space via a vertebral defect, or may be limited to an intraspinal component, which would be a radiological finding only. A lipomyelomeningocele is a lesion which extends from the dermis to the intraspinal space, and should be ruled out prior to surgical resection of a midline spinal subcutaneous lipoma suspected to be purely superficial to the fascia.[28]

Dimples in the sacrococcygeal area often present as a finding on routine baby checks and pathological lesions are characterised by specific findings. Normal dimples are seen in 4% of infants and are characterised by their location at the tip of the coccyx, which is palpable through the dimple. The characteristics of a pathological dimple include those that are midline, located above the natal cleft and discharging. Dimples that are deeper or larger than normal also merit investigation and should be evaluated as markers of a dermal sinus tract. Dermal sinus tracts are epithelial lined conduits between the skin and underlying planes from superficial fascia down as far as the intradural space. Dermal sinuses are primarily of the midline lumbosacral spine (90%), although cases exist of thoracic and cervical dermal sinus tracts[30] and tracts off the midline.[31,32] They are believed to occur from failed separation between cutaneous and neural ectoderms – ie a failure of dysjunction.[17] Dermal sinus tracts may be associated with dermoids and less commonly with epidermoids and rarely teratomas.[17] Undetected, dermal sinuses can lead to meningitis and progressive neurological deficits. All children with recurrent meningitis should be assessed for a dermal sinus tract.

Midline lumbosacral skin discolouration (red or brown) or frank purple vascular malformations that are most worrisome are hemangiomas, which can be large and may be associated with other markers of dysraphism, such as dimples or hairy patches. Raised pigmented vascular lesions are usually associated with dysraphism.

Finally, the finding of a tail or pseudo-tail near the coccyx, or a midline raised skin tag anywhere along the spine, has a strong correlation with occult spinal dysraphism. A true tail is extremely rare and composed of fatty tissue, vasculature, muscle, and nerve fibres. All of these lesions are associated with occult spinal dysraphism and should prompt further evaluation.[33]

Unfortunately, not all occult dysraphic states are associated with a cutaneous marker, and those without cutaneous markers may present later when other clinical manifestations of dysraphism have developed.

Neurological, orthopaedic, bladder and bowel manifestations of TCS

Sensorimotor dysfunction can be from a combination of upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction in the case of a conus lesion and pure LMN signs for lesions below the conus. This may present as lower extremity weakness and changes in sensation. Parents may report a delay in walking or changes in gait with the development of ataxia (worsening with fatigue or exercise), development of toe walking and regression of motor milestones. In addition, there may be contractures, alterations in tone, and muscle atrophy. The child may complain of back pain or radicular pain. Examination of the back may reveal scoliosis or abnormal lumbar lordosis in addition to the cutaneous markers described above.

Orthopaedic signs are essentially progressive deformities. They affect the lower limbs and/or the spine. Lower limb deformities are the result from imbalance between opposing muscle groups. These include pes cavus, varus, valgus and equinus deformities, tight Achilles tendons, clubbing, talipes, toe clawing, hammertoe, and leg length discrepancy. Spinal deformities can include scoliosis and sacral dysgenesis. These can be combined with deformity affecting individual vertebrae (segmental spinal dysgenesis) such as hemivertebrae, bifid vertebrae and laminar defects. Complications of orthopaedic lesions include low bone density,[34] respiratory dysfunction and spasticity. TCS may be demonstrated through a sudden deterioration after straightening or correction in scoliosis is undertaken before untethering. Sometimes, the orthopaedic complaints may be addressed surgically without suspecting the underlying neurological problems.

TCS may also present with urological manifestations. These can affect the structure and function of the lower and upper urinary tracts. The most common urological problems are neurogenic bladder with associated vesicoureteric reflux, overflow, recurrent urinary tract infections, stones and changes in continence. Presentation can be either with failure to attain continence or new onset incontinence. It may be subtle, with incomplete voiding, urinary frequency, stress incontinence and nocturnal enuresis.[35] Up to 25% of children with occult dysraphism will have uncoordinated detrusor and sphincter activity, that can lead to permanent renal damage via high bladder pressures and recurrent urinary tract infections (UTIs).[36] Sphincter function should be investigated early to avoid these complications.[36] Other urological problems associated with spinal dysraphism include cryptorchidism, renal agenesis, horseshoe kidney and less commonly cloacal and bladder exstrophy.[37]

Bowel dysfunction without bladder involvement is rare in dysraphism.[38] It may present with constipation or fecal incontinence. Rarely, imperforate anus may be present. Low and high anorectal malformations are associated with spinal dysraphism but are not usually directly visible without imaging.[39,40] The finding of any of these signs and symptoms should prompt further evaluation into the possibility of spinal dysraphism as the etiology. Sometimes, urogenital, hindgut and dysraphic spinal pathologies can constitute one of the genetic syndromes, such as VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities), OEIS (omphalocele, exstrophy of the cloaca, imperforate anus, and spinal defects) and Currarino's triad (anorectal malformation, a sacral bony defect and a presacral mass).

Although it is well documented that sexual dysfunction can be a consequence of tethered cord and a complication of any treatment for it, the psychosexual effect of tethered cord is a poorly explored area, although from what evidence is available, only half these patients are satisfied with their sex life, mainly inhibited through incontinence and poor self image.[41]

Diagnosing tethered cord syndrome

The diagnosis of occult spinal dysraphism can be a challenging one to make, as the differential diagnosis is wide. The benefit unique to GPs is that of familiarity with the medical history of the child and family over time. Work up of TCS includes a thorough physical examination and neuroimaging. The physical examination is centred on cutaneous findings along with neurological, orthopaedic and sphincter features of cord tethering.

In addition to physical examination, concerns regarding this possibility should be evaluated with radiological studies. A spine x-ray can reveal bony abnormalities associated with a spinal dysraphism. However, it will not reveal any cord anatomy and causes unnecessary radiation exposure. For this reason, x-rays are obsolete now in the assessment of occult dysraphism. Ultrasonographic exam before the age of three months has been useful to examine the level of the conus and identify obvious dysraphic lesions. In addition, ultra-

sonography provides real time data and pulsations of the cord can be documented.[42] But Magnetic Resonance Imaging is considered to be the "gold standard" in the investigation of spinal dysraphism. Absence of an abnormality on plain radiograph or with ultrasound evaluation in the face of a cutaneous marker or clinical findings should prompt further evaluation. If evidence of spinal dysraphism is found, a whole cranio-spinal MRI should be performed to identify any associated Chiari malformation, syringomyelia or hydrocephalus.

Options for managing TCS

Asymptomatic occult dysraphism is typically managed with regular outpatient follow up and active monitoring for orthopaedic, neurological and bladder/bowel changes that may suggest development of the tethered cord syndrome. The management of patients with occult dysraphism and clinical evidence of tethered cord syndrome is controversial and there is no level 1 evidence favouring a particular surgical approach or timing of surgery. The vast majority of surgeons would operate if the patient develops a new deficit related to tethered cord. Surgery is clearly indicated for those lesions placing the child in immediate danger, such as dermal sinus tracts associated with meningitis. The risks of untethering surgery are low when performed by an experienced Paediatric Neurosurgeon in a neurosurgical centre accustomed to this type of surgery. It is for these reasons that patients with radiological features of dysraphism will almost universally be referred for consideration of surgery. The case for prophylactic surgery is debated in the literature and is not undertaken in most centres on intact patients; although there is some evidence that surgery early in the course of clinical presentation, radical resections and surgery in children under the age of two years may be associated with favourable neurological outcome.[43,44]

In patients who undergo surgical management, the primary goal of the repair is to untether the cord and preserve or improve function. The secondary goal is the repair of the other associated anomalies available within the surgical exposure, such as lipomas and sinus tracts that currently or could in future contribute to tethering of the cord. This procedure may not extend to total resection of these anomalies if they are not responsible for the traction and tethering on the cord.

In surgery, patients are positioned prone and a midline incision is made centred over the area of pathology. The surgical approach tracks the abnormality from the skin, when present, through potentially abnormal subcutaneous tissues, fascia, bifid structures, and into the spinal cord or the filum terminale anomaly. The remainder of the operation focuses on the anatomical untethering of the attachments between the spinal cord and surrounding structures. Once the spinal cord is untethered, dural closure and closure of the overlying tissues is performed. The procedure is usually performed in a latex free environment to avoid sensitisation.

Spinal cord untethering is routinely performed under intraoperative neurophysiological motor tract and nerve root monitoring to allow stimulation of neurologically active structures and differentiation between adhesions that are functional from those that are not.[45] Sensory potentials are of limited value.[46] As complete a resection of the dysraphic anomaly causing TCS as possible should be performed to avoid retethering. The complication rate is quite low with experienced Paediatric Neurosurgeons. In a series of 238 cord lipoma resections, the incidence of neurological and urological complications was 4.2% and that of CSF leaks was 2.5%.[47] In complex cases, only partial untethering may be possible.[47]

Active monitoring of conservatively managed and post operative patients is best performed by a multidisciplinary team composed of a Paediatrician, Neurosurgeon, Urologist, Rehabilitation Physician, Orthopaedic Surgeon and Physiotherapist. Monitoring consists of serial neurologic exams, imaging if new clinical features develop, orthopaedic follow up, and evaluation of bladder function. Serial urological exams with urodynamic evaluation provides an objective tool for the monitoring of abnormalities.

The role of the multidisciplinary team in the long term care of TCS patients

Issues presented to the care team in the immediate post-operative period are primarily those of wound integrity and hygiene. In children, especially those with low-lying lesions, wound infection becomes a significant risk. There is no evidence supporting prophylactic post operative antibiotics.

Another serious risk is that of wound breakdown and/or cerebrospinal fluid (CSF) leakage. Children may be placed on flat bed rest for 48 hours or more postoperatively to reduce the CSF pressure in the lumbar canal. The duration for maintaining a flat positioning is controversial. A longer period is often necessary after a tenuous dural repair. Open CSF leak out of the wound should be addressed with some urgency for fear of infection leading to meningitis. The CSF leak may however be contained under the skin in a pseudomeningocele. In this scenario, symptoms of a low-pressure headache may be present. External pressure dressings to obliterate subcutaneous dead space, CSF diversion or operative wound revision may need to be performed.

Despite surgical repair, a child with occult spinal dysraphism and/or tethered cord syndrome needs to be on close follow up throughout his or her life. The success rate of untethering is dependent on the cause of tethering, with more complex aetiologies making recurrence more likely.[48] Most patients, after surgery, improve or have symptoms that stabilise. On the other hand, some (0-5%) may deteriorate. Deterioration is, as with the initial diagnosis of tethered cord syndrome, a clinical diagnosis[49] and revision surgery focuses on identification and division of adhesions followed by a tight dural closure or duraplasty.[48,49] Endoscopic division of adhesions may be performed by an experienced Paediatric Neurosurgeon.[50] The MDT role is that of coordinating care as the child grows into adulthood. Children should be evaluated for signs of retethering, which has an associated lifetime risk of approximately 10%, higher for those in the subset with more complicated anatomical repairs.

Tethered cord patients are a heterogenous group of individuals in terms of their biopsychosocial care needs.[51] Patients with associated hydrocephalus and a CSF shunt in situ are likely to have a greater biopsychosocial burden than patients without a shunt.[52] This is due to any cognitive impairment from cranial pathology and also from shunt related complications. Long term musculoskeletal consequences of tethered cord include joint contractures, skin ulceration, spasticity, muscle wasting, chronic pain and gait disturbance. These translate into a variable degree of physical impairment and functional disability. Management of these requires input from Physiotherapists and Occupational Therapists. Close liaison between therapists, caregivers and educational institutions can be used to maximise the child's participation in school activities. Care needs associated with a neurogenic bladder include training in home catheterisation, voiding techniques and regular follow up to monitor renal function. A number of non surgical and surgical strategies exist for the neurogenic bladder and bowel including enemas, stomas and bladder suspension.[36] Urology specialist nurses and continence nurses can teach catheterisation, advise on hygiene and work with patients and their families to minimise the complications and social stigma associated with continence difficulties. Women with tethered cord need specialised care during pregnancy.[53] In addition to the physical care requirements of the spina bifida patient, there are significant psychological and social aspects affecting the families of patients. A meta-analysis of 15 studies addressing parental psychological adjustment to spina bifida highlighted awareness of maternal psychological stress in particular.[54] The involvement of Pain Physicians and Psychologists should be considered.[55] A family centred rehabilitation model can address the needs of the family unit as well as the individual,[56] but independently addressing the psychological care of the family, so it does not become entirely focused on the progress of the child.[57]

Throughout the child's life, his/her normal development must be emphasised. This can truly be a challenge to the family faced with chronic health care issues. Stress should be

placed on emphasising the normalcy of the child, particularly the normal cognitive development (in cases without co-existent cranial pathology that causes cognitive impairment), the need for normal treatment in relation to other children in the household, and the awareness of the family to the "vulnerable child" trap. Despite our inherent desire to protect the child from unnecessary difficulties or challenges in life, we may unfortunately contribute further to the handicap by doing so.

Conclusion

The finding of a midline spinal dysraphic defect in a child is often subtle and can be missed. Cutaneous lesions can, however, represent a marker of an occult spinal dysraphic state and therefore suspicious lesions need further evaluation. The necessity of evaluation is due to the possibility of a spinal dysraphic state that can lead to the clinical entity of tethered cord syndrome. This diagnosis, its subsequent evaluation and management requires a multidisciplinary team, headed by the child's primary caregiver. Management options continue to be debated as not all low-lying spinal cords progress to tethered cord syndrome. Regardless, the role of the General Practitioner and the Paediatrician in the initial evaluation and communication to families of these possibilities, and his/her awareness to the impact of these diagnoses is critical in the optimisation of the child's physical and developmental health. ◆

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The Association of British Neurologists Annual Meeting 2014

Conference details: 6-9 May, 2014; Cardiff, UK. ***Report by:*** [1]Jason Chai, [1]Lloyd Evans, [1]Alethea Tang, [2]Thomas Hughes. [1]Cardiff University Medical Students [2]Department of Neurology, University Hospital of Wales.

As Cardiff medical students we were privileged this year to have the Annual Meeting of the Association of British Neurologists (ABN) hosted in the spectacular Millenium Centre in Cardiff. Brilliant minds from across the country and abroad gathered to share experiences in research and clinical practice with a real focus on inspiring the younger generation to pursue neurology. The venue provided state-of-the-art lecture theatres and ample space for mingling and discussion.

The meeting began with a Student Roadshow and Specialists' Registrar teaching programme opened by the ABN President Dr Geraint Fuller who delivered a lecture entitled "What neurologists do and Why?". The President likened a Neurologist to Sherlock Holmes, but with added empathy and better communication skills! He used case scenarios to capture the thought processes required by a Neurologist, emphasising the importance of a good history and clinical examination to deduce the "Where?, What?, and Why?" of the clinical problem; these themes were reinforced by the virtual case scenarios (Dr Joe Anderson), and an overview (Dr Alex Foulkes) of a career in neurology.

There were also student and junior doctor presentations including a project about the expression of a mitochondrial gene as a potential biomarker for Alzheimer's disease. Later in the afternoon Professor Huw Morris described highlights from ongoing research in neurology which included work on brain plasticity, neuropsychology, and unravelling the molecular mechanisms of neurological conditions.

Participants came together for the concluding session of the day ("How to get ahead in research"), in which the speakers (Dr Ed Fathers, Dr Masud Husain, Professor Phil Smith and Dr Will Whiteley) drew on their practical experience and knowledge of research and clinical neurology. They entertained and informed participants with simple but sound advice e.g. not more than five main points in a 40-minute talk, being clear and precise when writing, the time taken to complete a grant application (one estimate was six weeks), and keeping a balance between "play-safe" and "blue-sky" research.

The main conference began on the 7th May with the welcoming of delegates by Dr Fuller and the ABN President Elect Professor Phil Smith. There followed a feast of teaching including the neurological aspects of Intensive Care Medicine, Rheumatology and Haematology. Parallel sessions on Epilepsy and Multiple Sclerosis, and on Neuroinflammation and Movement disorders ensured that the subspecialties within neurology were covered. These teaching sessions were eye-opening and highlighted how clinical neurology is not limited to diseases originating in the brain and nervous system.

The afternoon session started with Professor Martin Samuels, from Harvard Medical School who delivered the Gordon Holmes lecture entitled "How Neurologists Think – What My Errors Taught Me". Using case presentations as examples, he described some common diagnostic pitfalls. His candid assessment of his own errors was inspiring. This had to be the highlight of the day, having an eloquent and esteemed clinician share his experience on an issue that is relevant and applicable to clinicians at all stages of training.

New on the programme this year was the Specialist Interest Groups in which delegates were able to meet and engage with like-minded colleagues. Groups were given the opportunity to plan in advance the content of their meetings which ranged from talks to videos and case-presentations, creating an ideal platform for intellectual discourse and the building of research networks.

The day concluded with a drinks reception and the ABN Trainee dinner.

The following day started with the poster exhibition. Of note was a case study on Melkersson-Rosenthal Syndrome, a study of the proportion of posters at ABN conferences that proceed to successful publication compared to other specialties in comparable meetings, and one entitled 'You Cannot be Sirius'; Sirius is an emerging legal-high with effects on the central nervous system.

The morning session included lectures by Professor Paul Morgan (the immunology of MS), Professor Neil Robertson (MS research within South Wales) and Professor Anne Rosser (stem cell transplantation). The lectures were of high quality and gave the audience a glimpse in to the future of the interaction between basic science and clinical neurology. They outlined the huge amount of work that goes on 'behind the scenes', and whetted our academic appetite.

After lunch, in the Shape of Training (SoT) debate, Dr Richard Davenport explained that the SoT plan would be detrimental to neurology, particularly because the time spent in specialty training before obtaining a certificate of specialty training would be shortened. Dr Tom Hughes concurred with this view but argued that more time spent engaged in general medicine is potentially very advantageous to specialty training. A show of hands showed overwhelming support for the view of Dr Davenport.

The final day began with the much anticipated case presentation competition. The seven cases included varicella vasculopathy and the 17 syndrome. In each case the relevant neuroanatomy was well described as was the effect of pathology on function. The winner was Dr Madhu Ramamoorthi who presented a case (entitled "It's no laughing matter") of myeloneuropathy secondary to nitrous oxide poisoning.

After coffee, Professor Matthew Kiernan described how good clinical observations and sound laboratory research are providing us with insights in to motor neurone disease and plausible theories for the mechanism of this disease. The lecture showed how collaborative work spearheaded by clinical observations has helped us start to understand this disease.

Professor Mary Reilly followed with an equally engrossing account of the clinical and genetic aspects of peripheral nerve disease including a useful description of algorithms to diagnose the commoner inherited neuropathies. She emphasised the central role of a detailed clinical history and examination, without which a genotype is difficult to interpret. This highlights the importance of honing history taking and examination skills which are just as important now as they were before the advances in genetics.

Throughout the conference, we were able to experience first-hand how neurologists think and approach problems; this was very well demonstrated in the clinicopathological conference during which Dr Graham Lennox gave a master class in how to think when confronted with difficult clinical cases. This is a way of thinking that should be made clear in all specialties and one that should be built upon from the early years of medical school.

The conference was an invaluable experience for students particularly because the specialists did not intimidate us but eagerly educated and inspired us. Despite the neurosciences being one of the most complex subjects, we have certainly been persuaded to enjoy this complexity and revel in its intricacies.

Useful websites and references

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A GP perspective

Report by: Dr Carol Amos, GP Monmouthshire, Wales, GP Appraiser and Tutor, Welsh Deanery.

I attended the Association of British Neurologists 'Need to Know' Neurology afternoon course for GPs on Tuesday 6th May 2014 in Cardiff and found the presentations to be uniformly interesting and relevant for general practice. Indeed I filled a complete notepad with personal notes from the talks which is a good indication to me of the wisdom imparted!

The meeting was chaired by Dr Alistair Church, a local GP and part-time Neurologist. He had obviously primed the presenters to make the sessions of practical use to GPs with information for our needs for daily practice. The long waiting times for Neurology specialist consultations make this an essential part of any educational workshop.

The first session was on Parkinson's Disease and Tremor by Dr Ralph Gregory. He described the different presenting symptoms and signs and interestingly the very early premonitory symptoms in PD such as loss of smell which can start many years before motor symptoms. The close liaison in particular with specialist nurses appears to be an essential part of PD management for the GP, especially as the advice is not to delay treatment in order to avoid (as much as possible) effects on quality of life.

The talk on dizziness by Dr Geraint Fuller was stimulating and showed the value of video access nowadays for looking at clinical signs and examination techniques online.

Dr Phil Smith talked about epilepsy and blackouts and differential diagnoses with practical advice on how to distinguish one from another. The value of any witness statements was emphasised and the need to exclude cardiac syncope such as with the long QT patient. It was interesting to see video accounts of patients describing their symptoms and the fact that the 'way' the patient tells the history is often important in making the diagnosis. I am not convinced I could exclude such organic causes without further specialist input but this was an educational insight into how to begin to clarify the diagnosis.

Dr Lionel Ginsberg presented his talk on Stroke versus TIA. His suggestion that a TIA would be better described as a 'non disabling stroke' makes sense and fits with local thoughts on prophylactic medication for a 'TIA' patient. Speed for carotid endarterectomy for the TIA patient was stressed as well as thrombolysis for the stroke patient. It was very useful to look at the list of symptoms and signs which help in differentiating migraine and transient epileptic amnesia from a TIA.

Hints on Headaches by Dr Richard Davenport brought migraine clearly into focus as well as cluster headaches as one of the Trigeminal Autonomic Cephalgia type headaches. A list of useful websites and the symptomatic 'staircase' (ladder) for treatment options was given.

Numbness and Tingling by Dr Gareth Llewelyn was our last session. This was a lively presentation so none had the same from their seats! The update in anatomy of the trigeminal nerve distribution was useful as was the reminder to exclude diabetes in patients presenting with truncal tingling sensations.

All in all: a very good afternoon. Many thanks to the presenters, Alistair and to ABN. ◆

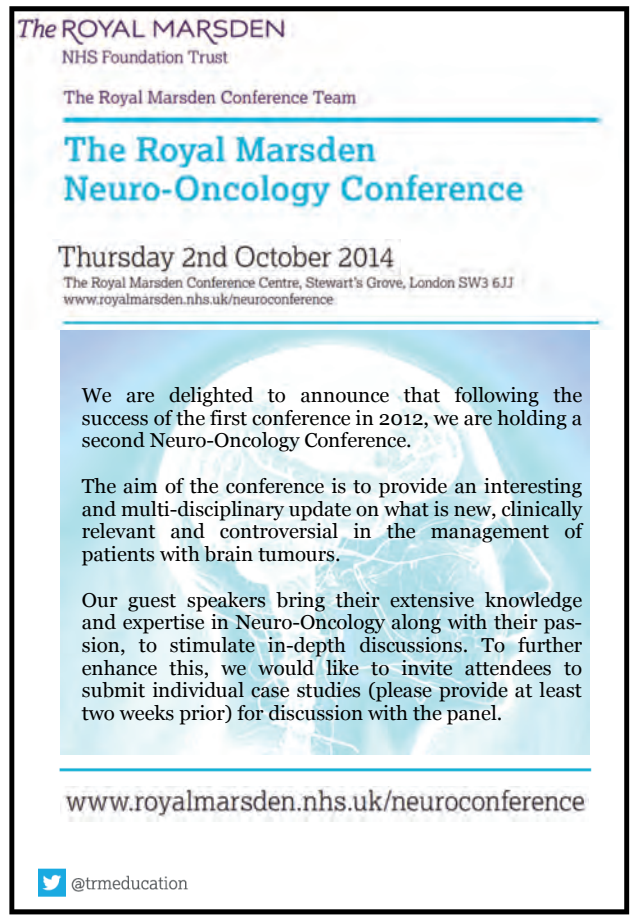
Neurology 2015: leading edge neurology for the practising clinician

Conference details: 25-27 March, 2015; London, UK.

The course, for Consultants and Senior Trainees, which is held annually, aims to provide a comprehensive update on the practical hospital management of neurological disease. The emphasis is on contemporary diagnosis and therapy in the clinical setting, and on the modern clinical practice of neurology. The plenary sessions are: therapy in acute neurology; neuromuscular diseases; headache and Parkinson's disease; difficult therapy areas; neuropsychiatry and dementia; stroke. There is a 'Nobel Lecture' by the 2014 Nobel Laureate for Medicine, Jim Rothman. The programme also includes video sessions, a clinico-pathological conference, and a 'Town Hall' session on commissioning led by Prof Patrick Venables. We expect the course to carry 15 CPD points.

An extensive course book will be provided, providing background material on each topic. There is also a pre-meeting half-day for trainees on 'Cramming for the exit exam' on Wednesday 25th March 2015 aiming to assist those taking the exam in the future. Registration fees are kept very low, in order to make the course accessible for as many as possible. The meeting is intended to be didactic but also fun and entertaining, and a great opportunity to network and meet old friends and colleagues. ◆

For details of the programme and for online registration, please go to:
http://www.ucl.ac.uk/ion/articles/courses/neurology



The Keele Course on Headache Disorders

Conference details: 19-21 June 2014; Keele University, UK. ***Report by:*** Dr Tom Button, Specialty Registrar, Norfolk & Norwich University Hospital.

To paraphrase, the general neurologist who is tired of headache is tired of neurology. However, I imagine all of us have felt a little worn when seeing the polysymptomatic patient rereferred with intractable headache. Nevertheless, headache patients are part of the reason I became a neurologist. When a house-officer in Sheffield, a consultant wisely told me that one might do worse than choose a specialty on the basis of how one could cope with the boring parts of the job (his words not mine). He pointed out that every patient with headache is different and that one must always listen to their story – in contrast to specialties in which one can treat the patient with scant regard whilst managing their figures – be that creatinine, blood pressure or peak flow (friends who are renal physicians etc will hopefully forgive my calumny). Certainly, when a primary headache consultation goes well, we all enjoy the satisfaction of knowing that how we gave our explanation and negotiated the plan was as important to the patient as the promise (or not) of the scan and tablets.

I should begin my report by saying how much I enjoyed the course and how confidently I would recommend it. I will outline the topics covered and some learning points that stood out for me.

The course opened with a practical guide to acute headache in the emergency department – not just subarachnoid haemorrhage – and went on to cover the most intractable of chronic headaches. Migraine was covered in appropriate detail from pathophysiology to current and future management; summarising it as a disorder of brain pain processing, with evidence for the molecular pathways from current and future treatments. Calcitonin gene related peptide (CGRP) release from trigeminal ganglion culture is inhibited by triptans and CGRP antagonism shows efficacy in migraine.

Typical of the course, this was excellent revision of core material with an ample sufficiency that was new to me. There were also sessions on the other major primary headaches. Excellent case based sessions were well planned to give a structured approach to spotting the red flags for secondary headache – for example, episodic headache and visual loss, initially attributed to migraine aura but not consistent with this because aura is binocular – and this was monocular acute angle closure glaucoma. Alex Sinclair, Birmingham, gave an excellent overview of idiopathic intracranial hypertension from diagnosis to management. As with the majority of the course, this lecture was accompanied by a useful handout.

So, very artificially choosing from much excellent material, my top three learning points: Acetazolamide shows no evidence of clinically significant benefit in two studies in idiopathic intracranial hypertension – so we are free to use better tolerated and symptomatically superior agents.

A reminder of the MHRA decision that domperidone 20mg PO TDS is contraindicated due to arrhythmic risk.

Paroxysmal hemicrania can look like cluster headache – perhaps always try indomethacin.

It was interesting to hear that this was the first year in which consultants have outnumbered registrars among the delegates. Perhaps they would have been struck by a different range of learning points, however, the delegate mix certainly highlights the quality of the course. To conclude, especially for those of you who have skipped the body of my report, suffice it to say that I would heartily recommend the Keele Headache Course. ◆

Rehabilitation in MS 2014

Conference details: 6-7 June, 2014; Brighton, UK. ***Report by:*** Ali Whittam, MS Trust.

In early June, the MS Trust co-hosted the 2014 RIMS (Rehabilitation in MS) Conference alongside University College London Hospitals Foundation Trust. This is the first time RIMS has been held in the UK and the theme of the conference was "Supporting behaviour change, linking science to clinical practice." The conference gave the 326 delegates from Europe and beyond the opportunity to learn, share best practice, network, and hear key clinical and opinion leaders in the field of MS. As well as originating from 26 different countries, the delegates represented a wide variety of professions including MS nurses, physiotherapists, occupational therapists, GPs, psychologists, social workers and speech and language therapists.

Although the ultimate goal is to find treatments that will delay and prevent progression, Professor Thompson strongly believes that good quality rehabilitation and symptom management trials are needed to improve the quality of life for those with progressive MS...

Factors influencing behaviour change

The conference opened with Jared Bruce, University of Missouri, USA. He discussed the poor adherence rates to MS treatment, with 40-50% of patients failing to adhere after two years. He looked at some of the cognitive, emotional, lifestyle and medical issues that can contribute to this including anxiety and depression. He went on to explore avenues for improving adherence to both medical and behavioural rehabilitation interventions.

The patient's perspective: what is behavioural change about and how does it manifest in 'real life'?

In a first for RIMS, two people with MS were invited to give their perspective on the reality of being given a diagnosis of MS, the challenges it brings to everyday life, and how they negotiate the upsets to restore and empower their lives. This session was extremely well received by the audience. Shana Pezaro, Trustee, the Federation Centre for Independent Living, discussed how different forms of exercise including squats and half-marathons have helped her manage her current health. She described how it had both helped her lose weight and transformed her confidence, to the extent that she started dating again. Emma Rogan, Project Coordinator, European MS Platform chose to speak about how taking care of your mental wellbeing was equally important to help you build resilience for the years ahead.

RIMS Honorary Lecture

The RIMS honorary lecture was provided by Professor Alan Thompson, Dean, UCL Faculty of Brain Sciences, University College London. He described the formation of the Progressive MS Alliance to address the needs of people with progressive MS, who constitute over 50% of the MS population. Management of progressive MS currently focuses on rehabilitation and symptom management as there is no effective treatment to slow or stop progression. However, there is a decided lack of studies focusing on this field, therefore the Progressive MS Alliance hopes to encourage innovative studies that will address both cognitive and motor dysfunction. Although the ultimate goal is to find treatments that will delay and prevent progression, Professor Thompson argued that good quality rehabilitation and symptom management trials are also needed to improve the quality of life for those with progressive MS.

Other plenary sessions

Rona Moss-Morris, from King[1]s College, London, discussed a cognitive behavioural therapy (CBT) programme designed to assist people with MS adjust to their diagnosis, and a mindfulness programme developed for people with progressive MS. Klaus Pfeifer, University of Erlangen-Nurnberg, Germany, described the development of a "Behavioural Exercise Therapy" programme to promote physical activity in people with neurological conditions. Paul van Asch, from the National MS Center in Belgium, presented a review of the many international sporting events organised by "Move to Sport". This is an organisation that aims to change people's ideas about sport and MS, by providing education sessions for health professionals, and sport and fitness coaches for people with MS to enable them to participate in sports in their own environment.

Posters

Nearly 100 posters were displayed at conference on a wide variety of topics. Platform presentations included health management, the economic burden of MS, bladder and bowel function and exercise treatment. All other researchers who had posters accepted were given one minute to sum up their research findings in the "speed poster presentation" slots, which proved to be both lively and informative sessions.

Prizes

The prize for the best oral presentation went to Jon Marsden, UK for his talk on the "Effect of localized lower limb warming and cooling on neuromuscular impairments and functional ability." The prize for the best poster presentation went to Paul Taylor, UK for his poster "A comparison of external and implanted FES for correction of dropped foot in MS."

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th October, 2014

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
http://www.redpublish.co.uk/courses
E. info@redpublish.co.uk

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

Stoke, Emotional Processing and Social Participation
26 Sept, 2014; Ely, UK
www.communitytherapy.org.uk/events.html

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

October

Neuro-Fatigue: Management of Fatigue in People with Neurological Conditions
Thurs 2 Oct, 2014; London UK.
www.communitytherapy.org.uk/events.html

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

Making Sense of the Muddle: Understanding the Dysexecutive Syndrome
24 October, 2014; Ely, UK
www.communitytherapy.org.uk/events.html

Fatigue and Sleep Disorders following ABI
24 October, 2014; Ely, UK
www.communitytherapy.org.uk/events.html

November

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

Managing Patients' Cognitive Impairment
10 November, 2014; London, UK
www.communitytherapy.org.uk/events.html

22nd Annual Meeting of the European Charcot Foundation
November 20-22, 2014; Baveno, Italy
www.charcot-ms.org

Sleep Disorders and Fatigue in Neurology
26 November, 2014; Tonbridge, UK
www.communitytherapy.org.uk/events.html

Flying in the face of RNA foci: RAN peptide toxicity in ALS

Reviewer: Dr Jemeen Sreedharan, Dept of Neurobiology/ Neurology, University of Massachusetts Medical School, Worcester, USA.

The commonest known cause of ALS (and a common cause of FTD) is a huge intronic hexanucleotide (GGGGCC) repeat expansion in the gene C9orf72. The normal role of C9orf72 is unknown, though knockout mice (so far) seem normal, suggesting that the repeat expansion causes a toxic gain of function rather than a loss of function. But how does an expansion of hundreds to thousands of GGGGCC motifs cause neurodegeneration? Two main hypotheses have been proposed. Firstly, the RNA transcript composed of repeats forms foci within the nuclei of neurons, glia and even peripheral cells such as fibroblasts. Similar foci in myotonic dystrophy are known to sequester muscleblind, a critical RNA binding protein, whose subsequent loss of function leads to the disease. The hunt for the key proteins sequestered in C9orf72 RNA foci has so far led to inconsistent results between labs. Furthermore, it has not been convincingly shown that these RNA foci are actually directly toxic.

The second model proposes that protein toxicity underlies C9orf72 ALS and FTD. Last year it was shown that the RNA expansions, despite being intronic, are actually translated into dipeptide repeat (DPR) proteins through an unusual mechanism termed Repeat Associated Non-ATG (RAN) translation. DPR proteins were found sequestered in the brains of patients with ALS and FTD and marked C9orf72 expansion carriers out from sporadic patients. However, as with the RNA foci, it was not clear if these peptides are toxic. The work of Adrian Isaacs' group (Mizielinska et al Science 2014) has helped to shed light on this question.

Isaacs' team created artificial C9orf72 RNA repeat expansions (not an easy thing to do as the GGGGCC repeat is very unstable) and then expressed these in cells in vitro and also in vivo using flies. They found that these expansions formed RNA foci and were also translated into DPR proteins. These animals died prematurely. What they also did was to express modified RNA expansions in which the repeats are sparsely interrupted such that RNA foci still form, but the RNA is not translated into DPR proteins. These animals, strikingly, appeared normal. They also did the inverse, expressing DPR proteins using RNA sequences that were unable to form foci, and found that these animals died. This data collectively implicates protein rather than RNA in C9orf72-ALS-FTD.

Although there is likely to be a rush towards understanding DPR toxicity following this and another recent paper (Kwon et al Science 2014), RNA toxicity remains a possibility. One should also be aware that the fly does not have an obvious orthologue of C9orf72 and validation of dipeptide toxicity in a mouse is eagerly awaited. And, aside from the RNA and DPR proteins, what on earth does C9orf72 actually do under normal circumstances? Its biology remains unexplored.

Kwon I, Xiang S, Kato M et al. Poly-dipeptides encoded by the C9ORF72 repeats bind nucleoli, impede RNA biogenesis, and kill cells. SCIENCE. 2014 Jul 31. [Epub ahead of print]

Mizielinska S, Grönke S, Niccoli T et al. C9orf72 repeat expansions cause neurodegeneration in Drosophila through arginine-rich proteins. SCIENCE. 2014 Aug 7. [Epub ahead of print]

Good with faces. Treating prosopagnosia

Reviewer: Dr Aidan Neligan, UCL Institute of Neurology, Queen Square, London, UK.

This month sees the publication of a large multicentre collaborative meta-analysis of data from 12 previously published or unpublished genetic cohort studies to identify potential variants that increase the risk of epilepsy.

Seizures and epilepsy was classified according to the International League Against Epilepsy (ILAE) terminology into genetic generalised epilepsy, focal epilepsy or unclassified epilepsy (where there was neither electro-clinical evidence for a focal or generalised onset or alternatively if there was evidence for both focal and generalised epilepsy). In total 40,789 people comprising 10,064 people with epilepsy and 30,725 controls from 12 cohorts were studied. In the all-epilepsy analysis two loci with genome-wide significance were identified ($p<1.66 \times 10^{-8}$). The first signal was located at 2q24.3, which is centred on the voltage-gated sodium channel gene SCN1A which has previously been associated with genetic epilepsy with febrile seizures plus (GEFS+) and the severe epileptic encephalopathy Dravet syndrome. A second signal for the all-epilepsy phenotype was located at 4p15.1 including the 3' end of the protocadherin gene PCDH7. This is a novel association not previously described with epilepsy. The PCDHT gene is a member of the cadherin gene family, which encodes for a calcium-dependent adhesion protein and is specifically expressed in the hippocampus and the thalmocortical pathways. Whilst the PCDH7 signal only achieved genome-wide significance for the all-epilepsy phenotype, it was

more strongly associated with generalised rather than the focal epilepsies.

Analysis of the generalised epilepsies included 2,606 people with epilepsy and 18,990 controls across eight cohorts. A single signal achieved the threshold of genome wide significance; this was located at 2p16.1, the interval containing the genes encoding the vaccine-related kinase 2 (VRK2) and Fanconi anaemia, complementation group L (FANCL). Variation in VRK2 has previously been postulated as a risk factor for schizophrenia and epilepsy. VRK2 is a serine-threonine protein kinase, which is involved in cell apoptosis and signal transduction. The other gene in the interval FANCL, which encodes for a RING-type E3 ubiquitin ligase in the Fanconi anaemia pathway, has not previously been associated with a seizure phenotype.

In the meta-analysis of focal epilepsy involving 28,916 individuals no single signal achieved genome-wide significance. Finally, the authors found that none of the identified susceptibility loci with nominal genome-wide significance were associated with prognosis or outcome of newly treated epilepsy.

The importance of such work is the demonstration that with cohorts of a large enough sample size, susceptibility loci for common epilepsies can be identified through the analysis of common variation. The authors correctly conclude that whilst this work may not have immediate clinical application, it provides useful pointers to the genetic architecture of the epilepsies, which may, in time, lead to clinically applicable biomarkers of seizure prognosis and outcome.

International League Against Epilepsy Consortium on Complex Epilepsies. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies.
LANCET NEUROL 2014;13:893-903.

CSI CRPS

Reviewer: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust, UK

Chronic regional pain syndrome (CRPS) is a poorly defined disorder that involves a range of clinical features including swelling, changes in peripheral temperature, dysasthaesia and weakness. It often occurs in a limb that has suffered some sort of trauma or other noxious insult, and may cause substantial impairment for an individual in terms of functional loss of activity through pain or weakness. It is now increasingly recognised that as well as CRPS occurring within the realm of mechanical injury, acute neurological insults (such as strokes) can precipitate a similar constellation of symptoms. Although in the past these may have been lumped within the broad category of "central neuropathic pain," this conceptualisation of the problem as a disorder of central pain perception probably oversimplifies the aetiology and means that opportunities for thinking about different clinical interventions are lost. The interaction between somatosensation, weakness, swelling and pain in an affected limb following a stroke are very complex and may be driven by the interaction between both mechanical and primarily neurological factors.

This study retrospectively reviews a large cohort of patients admitted following a stroke who went on to develop CRPS. CRPS was defined by diffuse limitations in uptake on a bone scan. While this is the diagnostic gold standard for the diagnosis, the possible contribution of motor weakness to bone density loss following a stroke is not considered. The cohort assessed all had somatosensory evoked potentials (SEPs) performed shortly following admission post-stroke, which allowed the authors to evaluate how the measured SEPs correlated with the later presentation of CRPS. The glenohumeral distance (on x-ray) was also measured in the acute stage which allowed a similar assessment of correlation of shoulder subluxation with the development of CRPS.

The researchers identified that absence of a median SEP was strongly correlated with the later development of CRPS as well as with shoulder subluxation. There is great difficulty in defining the role of shoulder subluxation in the development of CRPS per se. The researchers postulate that it is the severity of the motor deficit that predicts onset of CRPS, however it is never really defined how this suggestion could be supported.

Given the negative impact that the development of CRPS has on stroke rehabilitation, there is a need to consider its presence as soon as possible. Early and aggressive desensitisation and analgesia are associated with better outcomes, although there is obviously a need to firstly positively identify it. Despite the fact that this study does not adequately explain how absent SEPs may encourage the development of CRPS, it does remind the clinician of the importance of maintaining a high index of suspicion for this syndrome, particularly in patients where a stroke produces sensory impairment in a distal limb.

Han EY, Jung HY, Kim MO. Absent Median Somatosensory Evoked Potential is a Predictor of Type 1 Complex Regional Pain Syndrome. DISABILITY AND REHABILITATION. 2014;36(13):1080-4.

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