PAPER OF THE YEAR: MULTIPLE SCLEROSIS

Chosen article: ***Sodium Chloride Drives Autoimmune Disease by the Induction of Pathogenic Th17 Cells. Kleinewietfeld M, Manzel A, Titze J et al. Nature 2013; 496:518-52.***

Reviewer: Dr Alasdair Coles, Senior Lecturer University of Cambridge & Honorary consultant neurologist, Addenbrookes Hospital, Cambridge.

Multiple Sclerosis and salt

2013 has been the Year of Salt for multiple sclerosis. The high-brow gossip is no longer about vitamin D or veins, but humble sodium chloride.

For several years, Ken Smith and colleagues in London have been assembling a picture of the metabolic life of the demyelinated axon. It turns out that the innocent sodium ion, Na^+, can be a millstone around the neck of the struggling axon. As a nerve demyelinates, sodium channels spread from the nodes of (Louis-Antoine) Ranvier to redistribute along the length of the naked axon. So, when Mr Hodgin and Mr Huxley's action potential passes by, there is rather more sodium entry to the cell than there should be. The more sodium ions accumulate inside the axon, the more energy is required to get rid of them, and someday energy supply cannot meet demand and the lights go out. This can even be imaged: David Miller showed this sodium accumulation in people with progressive multiple sclerosis radiologically in Brain this July.

The news this year is that eating salt is bad for multiple sclerosis. David Hafler's team at Yale have shown that naïve T cells can be turned into nasty killer Th17 cells by swimming in salty water. Furthermore, mice who eat salty food (?) are particularly susceptible to experimental autoimmune encephalomyelitis (EAE), because bad Th17 cells have been switched on.

Why should salt have this effect? Well, lymph nodes normally have high salt levels; perhaps this activates Th17 cells, while they encounter antigen, and then the cells calm down in the lower-salt environments outside the node.

Should people with multiple sclerosis go on a low-salt diet? Well probably, to avoid hypertension and the like. But it is a little early to deny our patients the important morale-boosting effects of salted battered cod and chips.

PAPER OF THE YEAR: GENETICS IN ATAXIA

Chosen article: ***Ataxia, Dementia and Hypogonadotropism Caused by Disordered Ubiquitination. Margolin DH, Kousi M, Chan YM et al. The New England Journal of Medicine 2013; 368:1992-2003.***

Reviewer: Dr Sarah Wiethoff, Dr Joshua Hersheson and Prof Henry Houlden, Department of Molecular Neuroscience and MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London.

The Quickening Maze

Gordon Morgan Holmes first described the co-occurrence of cerebellar ataxia and hypogonadism in 1907 as a neurologist at The National Hospital for Neurology and Neurosurgery in London. Over 100 years later in 2013 a gene was identified causing a very similar phenotype of "Ataxia, Dementia and Hypogonadotropism Caused by Disordered Ubiquitination" by Margolin et al. published in *The New England Journal of Medicine*.

Using whole-exome sequencing and consecutive targeted sequencing of candidate genes Margolin et al identified digenic homozygous mutations in RNF216 and OTUD4, encoding two proteins in the ubiquitination pathway, in three affected siblings with consanguineous background. Compound heterozygous truncating mutations in RNF216 could be found in one additional unrelated patient as well as single heterozygous deleterious mutations in four other patients. The clinical phenotype comprised hypogonadotropic hypogonadism with defects at the hypothalamic and pituitary levels of the endocrine axis, as well as progressive ataxia and dementia with neuronal loss in cerebellum and hippocampus. Functional knockdown of the single genes and the combination of both induced a similar phenotype in zebrafish which could be rescued by nonmutant human RNF216 or OTUD4 messenger RNA. Ubiquitin-immunoreactive intranuclear inclusions were present in surviving hippocampal neurons.

The study sheds important light on the genetic underpinnings of the association of ataxia with hypogonadotropic hypogonadism by showing that mutations in RNF216 either solely or combined with mutations in OTUD4 can cause this clinical phenotype that was previously genetically unresolved. The published release of these two new genes prompted us to screen our clinical cohort of unresolved autosomal-recessive cerebellar ataxias for further affected cases. Surprisingly we identified a homozygous splicing variant in RNF216 in a patient with early adulthood-onset cerebellar ataxia from a consanguineous family which segregated within the family and was neither found in our in-house database of 300 exomes nor in the conventional open access exome databases. Interestingly, our patient did not have hypogonadotropic hypogonadism, nor dementia.

The description of two causal genes in the constellation of syndromes comprising ataxia, dementia and hypogonadotropism will open pathways further elucidating the importance of disordered ubiquitination in neuronal degeneration. Nonetheless, our findings show that even though the current study of Margolin et al. is solidly backed-up by functional data, one needs to remain open to the possibility of further phenotypic variability within the spectrum of ataxia and ubiquitination disorders.

PAPER OF THE YEAR: GUILLAIN BARRÉ SYNDROME

Chosen article:

- ***Jacobs BC. IGOS - International GBS Outcome Study***
- ***International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. Dodd CN, Romio SA, Black S, et al. Vaccine 2013; 31:4448–58.***
- ***IGOS Newsletter. https://www.gbsstudies.org/extended-newsletter***

Reviewer: Dr Simon Rinaldi, Academic Clinical Lecturer, Nuffield Department of Clinical Neurosciences, University of Oxford.

GBS: Strength in numbers

My paper of the year review includes one paper, two clinical trials, and a multi-centre observational study, united under the common theme of the year in Guillain Barré syndrome – international collaboration.

Ever since the 1976 "swine flu" vaccine was suspected of inducing GBS there have been anxieties that subsequent vaccines might also have this adverse effect. This was especially the case during the contemporary outbreak of a similar influenza strain (H1N1). In a study published earlier this year, the Global H1N1 GBS Consortium demonstrate the feasibility of international collaboration in assessing vaccine safety. An impressive 479 GBS cases were contributed by 15 countries, providing unprecedented power to assess this rare adverse event. Using a self-controlled case series methodology not reliant on accurate knowledge of underlying background incidence rates, the consortium report a relative increased incidence risk of 2 to 3 for GBS in the 42 days following H1N1 vaccination, translating to 1-2 excess cases per million vaccines administered. They were also able to show the time of peak GBS risk is 8-21 days post vaccination, as might be expected for a pathological mechanism likely to be driven by an IgG based humoral immune response. The at risk period chosen and the influence of seasonal infections, including influenza itself, can confound these estimates. Nevertheless, the study addresses these concerns using a number of different statistical approaches, and gives a consistent estimate of the risk of vaccination with respect to GBS. This has immediate utility in counselling patients who might receive vaccination, and in informing vaccination policies.

The bottom line is that this high quality evidence shows that the risk of GBS is low, and almost certainly outweighed by the protective benefits of vaccination.

Likewise, patients with GBS are often understandably anxious to know how long they will take to recover. Until recently, meaningful prognostication proved difficult. Another highly impressive ongoing international study aims to identify easily obtainable factors which

predict disease course at an early stage, building upon earlier excellent work from the Dutch GBS study group. The International GBS Outcome Study (IGOS) aims to collect detailed clinical data, along with serum samples and DNA, from 1000 patients with GBS. In the last year 100 centres over 13 countries have joined the study and approaching 220 patients have been included at the time of writing. This unprecedented international collaboration has great promise in improving prognostication, but also will provide an extremely valuable bio-bank for studying immunopathological mechanisms and genetic susceptibility. Moreover, IGOS will integrate with international multi-centre treatment trials, as has already begun with the International Second IVIg dose trial, and will underpin future studies of novel agents such as complement inhibitors.

The benefit of international collaboration for addressing key questions in GBS has already been well demonstrated, and as such the results from IGOS and related studies are eagerly anticipated. They seem likely to feature prominently in future 'paper of the year' reviews.

PAPER OF THE YEAR: NEURO REHABILITATION

Chosen article: ***Early cranioplasty may improve outcome in neurological patients with decompressive craniectomy. Bender A, Heulin S, Röhrer S et al. Brain Injury 2013; 27:1073-1079.***

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

Cranioplasty – What are you waiting for

The neurosurgical management of patients sustaining intracranial hypertension in the context of traumatic brain injury or stroke may involve decompressive craniectomy. The removal of part of the skull in order to prevent secondary brain damage through increasing intracranial pressure is no longer the esoteric procedure that it was once seen as. Because the procedure is almost always performed in emergency situations, the availability of well-planned double-blinded trial data is obviously somewhat limited. It is difficult, therefore, to apply a sound evidence base to decisions made in the acute environment on an individual patient basis.

Those who come through neurosurgical services having undergone a craniectomy may then undergo a cranioplasty, which involves either replacing the original skull flap which was removed or a titanium plate, fashioned specifically to cover the defect. Different neurosurgeons have different views around the timing of cranioplasty. Although some patients do develop sunken bone flaps with deteriorating neurological function secondary to shifts in intracranial contents, there is very limited information on the optimal timing for replacement of the flap and this remains a source of some frustration for patients and clinicians. The rather crude outcome measures employed in many surgical studies do not capture any meaningful change in consciousness levels following the procedure and it is seen as being of rather low-priority in the ongoing management of this patient group. There are many anecdotal reports and case series of significant improvements being engendered by undergoing cranioplasty, but very little outcome data on larger populations.

This German series follows 147 patients undergoing inpatient neurological rehabilitation who are, therefore, subject to regular clinical scrutiny and assessment. The series compares patients undergoing early (<86 days) and late (>86 days) cranioplasty in terms of their Barthel Index (BI), Functional Independence Measure (FIM) and Coma Responsiveness Scales (CRS). It is illuminating that the two groups were allocated operative intervention at times determined by "organisational issues and surgeon choice" rather than any specific clinical factor.

There was no difference in pre-operative functional level (BI) or age between the groups. Patients undergoing early (<86 days) cranioplasty had significantly better BI ($p<0.01$) and FIM ($p<0.05$) scores than the late intervention group at the time of discharge from inpatient rehabilitation. There were no differences in levels of awareness (CRS) at discharge. For all patients undergoing cranioplasty there were significant immediate improvements in function following the procedure as evidenced by gains in the BI ($p<0.001$) and FIM ($p<0.001$) in the first week afterwards. There were no differences in complication rate (bleeding, seizures, infection, stroke) between the 2 groups.

Unfortunately no mention is made of the effect on length of stay in rehabilitation or of the larger economic and social implications of functional improvements engendered by earlier intervention. Nevertheless, it does go some way to asserting what many professionals working in brain injury rehabilitation have suspected for some time; that postponing and delaying elective cranioplasty as a low priority procedure is clinically questionable.

PAPER OF THE YEAR: CLINICAL ASPECTS OF MND

Chosen article: ***Structural brain network imaging shows expanding disconnection of the motor system in amyotrophic lateral sclerosis. Verstraete E, Veldink JH, van den Berg LH et al. Hum Brain Mapp. 2013 Mar 1 [Epub ahead of print].***

Reviewer: Dr Martin R. Turner, MRC Senior Clinical Fellow and Honorary Consultant Neurologist, University of Oxford Nuffield Department of Clinical Neurosciences & John Radcliffe Hospital, Oxford.

ALS Imaging: An elegant model

At the time of writing, more than 1300 articles have been published with a 2013 date using the PubMed search term 'amyotrophic lateral sclerosis (ALS) or motor neurone disease'. The total for the year is expected to exceed 2000, and already represents more than 5% of the total number of publications in this field. An exponential growth in ALS research has been driven by advances in the understanding of the molecular biology, in particular the role of aberrant cellular RNA processing and protein handling. ALS shares clinical, pathological and now genetic features with frontotemporal dementia (FTD), with hexanucleotide repeat expansions in C9orf72 associated with nearly 10% of all apparently sporadic ALS and 25% of 'pure' FTD cases. The traditional concept of ALS involving a highly selective vulnerability of only upper and lower motor neurons is now untenable. ALS is a multiple system disorder in which the brain is consistently involved.

Beyond advances at the cellular level, there is a growing realization that to fully understand the pathogenesis of neurodegenerative disorders, not least how they are propagated in such stereotyped clinical patterns, requires the study of the brain and its downstream connections as a system. The development and analysis of resting-state functional MRI-defined networks is a growing area in this regard, but an allied strategy has been to apply network mathematical theory to the detailed white matter tract connectivity maps that may now be derived entirely non-invasively from diffusion tensor imaging (DTI).

Graph theory is based on 18th Century Swiss mathematician Leonhard Euler's solution to the Seven Bridges of Königsberg problem. The brain may be represented as a system of hubs (nodes or vertices), linked by tracts (edges or lines) defined using well-established tractographic techniques based on DTI data. The team from Utrecht, Netherlands applied this technique to twenty-four ALS patients scanned twice with a six-month interval, and compared to healthy controls. The paper initially elegantly outlines several possibilities for how their model consisting of 83 nodes and edges might change over time (Figure 1). Rather than the dogma of ALS pathology affecting only a fixed set of primary motor connections, their results demonstrate an expanding network of impaired connectivity over time, with notable involvement of frontotemporal lobe projections, entirely in keeping with clinical, histopathological and molecular insights.

The nature of spread of neurodegeneration is unclear, but a "prion-like" propagation between neurons is a candidate mechanism. The observation clinically and histologically of contiguous regional involvement in body territories certainly supports the view that structural connectivity is important in

defining this process in ALS, and the authors conclude that their results are consistent with this concept.

MRI has come a long way from greyscale histological images, and the "just a pretty picture" dismissal of DTI is entirely unjustified. Of course the validity of applying mathematical models, in particular graph theory, to biological systems as complex as the brain is highly questionable. The brain is clearly not an 83-node structure, and it will be challenging to find ways to validate such models. Clinical observations in conjunction with neurophysiological correlates (e.g. MEG) and traditional histopathological study, including the emerging field of post mortem DTI, offer potential.

These connectivity studies are not yet applicable to the single subject. However, I believe we have glimpsed the future of neuroimaging, particularly "systems-level neuroscience" in this article. A paradigm shift in the concept of neurodegeneration is underway, which will crucially include application of these techniques to pre-symptomatic individuals at high genetic risk. Advanced MRI is now at the forefront of the search for much-needed biomarkers that will be essential for the goal of a therapeutic era in ALS.

PAPER OF THE YEAR: PATHOGENESIS OF MOTOR NEURON DISEASE

Chosen article: ***Unconventional Translation of C9ORF72 GGGGCC Expansion Generates Insoluble Polypeptides Specific to c9FTD/ALS. Peter E.A. Ash, Kevin F. Bieniek, et al. Neuron 2013; 77:639–46.***

Reviewer: Professor Kevin Talbot, Nuffield Department of Clinical Neurosciences, University of Oxford.

Zooming in on C9orf72

Our understanding of the cause of two important neurodegenerative diseases underwent a step change in 2011 with the identification of an expanded hexanucleotide (GGGGCC=G4C2) repeat in the first intron of the C9orf72 gene as the most common mutation in familial ALS and FTD patients. Remarkably, as well as affecting 30-40% of familial ALS, FTD and ALS/FTD cases, the mutation is found in 7% of sporadic cases of ALS and 6% of FTD. Pathologically, C9orf72 mutation cases have TDP-43 positive inclusions, like those found in the majority of ALS and FTD-TDP patients, but also have atypical TDP43-negative inclusions. Since then the mechanism of toxicity of this mutation has been the subject of intense interest. As with myotonic dystrophy nuclear RNA foci can be detected using a probe against the G4C2 and the leading theory behind cellular toxicity is still therefore that these RNA foci bind ribonuclear proteins, interfering with post-transcriptional mRNA processing, presumably of genes with neuronal specificity. Other evidence, principally morpholino-induced knockdown in zebrafish, suggests that reduced levels of the C9orf72 protein, the function of which is currently unknown, might play a part in pathogenesis.

A third potential mechanism is suggested by a study reported in *Neuron* in 2013, implicating a novel kind of protein toxicity. The authors took the elegant approach of studying the repetitive sequence in the G4C2 expansion and hypothesizing that, although the expansion is in a non-coding part of the gene, the potential products of a non-canonical form of translation previously observed in other repeat disorders (SCA8 and myotonic dystrophy). Repeat associated non-ATG (RAN) translation is predicted to generate a series of dinucleotide repeat proteins, the number and variety of which depend on the frame in which translation occurs. To test this hypothesis they generated polyclonal antibodies by injecting GA, GP, and GR (glycine+alanine, proline or arginine) octamers as antigens, from the predicted RAN translation products of (GGGGCC)n transcripts in the three alternate reading frames. The resulting harvested serum was used to probe tissue from FTD and ALS patients and detected specific immunoreactivity, not present in other neurodegenerative disease. This highly novel and unexpected mechanism of protein production from a repeat expansion appears therefore to be pathognomonic of C9orf 72 ALS/FTD. Whether it is just a biomarker or has a mechanistic role in pathogenesis remains to be seen.

PAPER OF THE YEAR: TIC DISORDERS

Chosen article: ***Current Controversies on the role of Behaviour therapy in Tourette syndrome. Scahill L, Woods D, Himle M et al. Movement Disorders 2013; 28:1179-1183.***

Reviewer: Dr Hugh Rickards, Consultant in Neuropsychiatry, Birmingham and Solihull Mental Health Foundation NHS Trust. Birmingham. Honorary Reader in Neuropsychiatry, Birmingham University.

Tourettes: a renaissance of behavioural therapies?

Behavioural therapies for Tourette syndrome have been around for a long time. Armand Trousseau, who described this condition prior to Gilles de la Tourette himself, recommended a form of training based on a metronome which was, effectively, behavioural (Rickards et al 2010). In the latter part of the 19th Century and for most of the 20th Century, tic disorders were seen from a psychodynamic perspective. When we emerged from this with more biological ideas following Seignot's first successful treatment of tics with haloperidol (Rickards et al 1997), behavioural treatments were seen as threatening progress and, possibly, as dragging us back to a psychological narrative. Behavioural treatments were attempted in the 1970's in the form of massed practice, but did not really catch on. In the last 10 years however, a number of high quality randomised clinical trials have taken place which have shown behavioural treatments to be effective in reducing tics, at least in the short term. (Piacentini et al 2010. Wilhelm et al 2012).

The paper I have chosen reflects the controversies around behaviour therapy and uses evidence to place these therapies on a par with medications for tic disorders. The authors include two of the main researchers in the area (Woods and Piacentini) as well as senior figures from the US Tourette Syndrome Association. Table 1 in the paper directly contrasts the randomised studies of both drug and behavioural therapies. Subject numbers and duration of treatment tends to be longer in the behavioural trials with effect size being comparable but possibly a little lower in this group. Drop-outs were a little lower in the behavioural therapy trials suggesting better toleration.

The authors then go on to debunk what they regard as myths around behavioural therapies, particularly that they only work for mild tics, that they are too much effort, that gains are less durable or that "symptom substitution" occurs.

Finally, they tackle the idea that an effective behavioural therapy would lead to the "recasting of TS as a psychological, rather than a neurological disorder" by refuting this as a false dichotomy. Certainly, the last year has also seen advances in the genetics of the disorder, indicating differences particularly in the genetics of the histamine system (Karagiannidis et al 2013), showing that simultaneous understanding in both the biological and psychological domains is possible and desirable.

The renaissance of behavioural therapies in Tourette syndrome signifies a maturity in the conceptualisation of this disorder which has shifted from "organic" to "functional" and back again in the last 150 years. Finally, we might be shedding this false skin of dualism and moving forward in a more integrated manner.

References:

Support for the histaminergic hypothesis in Tourette syndrome: association of the histamine decarboxylase gene in a large sample of families. Karagiannidis I, Dehning S, Sandor P et al. Journal of Medical Genetics 2013. Jul 3 [Epub ahead of print]

Behaviour therapy for children with Tourette disorder: A randomised controlled trial. Piacentini J, Woods DW, Scahill L et al. JAMA 2010; 303:1929-1937

"Trousseau's disease" a description of the Gilles de la Tourette syndrome 12 years before 1885. Rickards H, Woolf I & Cavanna AE et al. Movement Disorders 2010; 25:2285-2289

Seignot's paper on the treatment of Tourette's syndrome with haloperidol. Rickards H, Hartley N & Robertson MM. Classic Text No.31. History of Psychiatry 1997; 31:433-436

Randomized trial of behaviour therapy for adults with Tourette's disorder. Wilhelm S, Peterson AI, Piacentini J et al. Archives of General Psychiatry 2012; 69:795-803

PAPER OF THE YEAR: EPILEPSY

Chosen article: ***Local cortical dynamics of burst suppression in the anaesthetized brain. Lewis LD, Ching S, Weiner VS et al. Brain 2013; 136: 2727-2737.***

Reviewer: Dr Mark Manford, Consultant neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospitals NHS Trust.

Unravelling burst suppression

Burst suppression of the EEG is an enigmatic state. In the past it has been argued that it is the Holy Grail of treatment in the treatment of status epilepticus. It is also seen in some severe pathological (comatose) states and yet little has been understood about what it is or what it means. Investigating it in animals with small brains provides relatively little opportunity to generate data meaningful for the human condition where cortical distances are much greater.

The authors took five patients who were being investigated for epilepsy surgery with intracranial EEG and made measurements of the burst suppression state, looking at the correlation of discharges across brain regions sampled and their temporal association as well as the time course and spectral frequency of the discharges. They found that burst suppression is not a uniform condition but that bursts sometimes occur in one place and not in others and that the closer to each other were the electrodes, the more likely they were to burst together, but even then not at precisely the same time. They also found that different regions were more or less likely to enter a burst suppression state with a given dose of anaesthetic and that the pattern was most consistent with the local prior metabolic state determining the likelihood of burst suppression. They hypothesise that a low metabolic activity predisposes to EEG suppression with intermittent escapes of the burst as metabolic state recovers slightly.

Their analysis suggests that the bursts represent the previous activity of that region of the brain, prior to the induction of burst suppression and spectral analysis of the bursts may help to determine when the underlying pathophysiological processes are recovering. The role of thalamocortical connections is important in generating this pattern but this study, with only cortical recordings, could not really assess their contributions.

This paper not only casts light on a conceptually difficult area in epilepsy but may also have significance for the treatment of the most refractory of epileptic states if methods for regional and spectral analysis of the burst suppression EEG were to be developed.

PAPER OF THE YEAR: INTRACEREBRAL HAEMORRHAGE

Chosen article: ***Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. Anderson CS, Heeley E, Huang Y et al. INTERACT2 Investigators. The New England Journal of Medicine 2013;368: 2355-65.***

Reviewer: William Rutherford and Rustam Al-Shahi Salman, Division of Clinical Neurosciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh.

ICH: Under Pressure

Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) has a worse outcome than ischaemic stroke and hitherto no specific treatment. Neither the haemostatic drug recombinant activated factor VII nor surgical evacuation appear to be effective for acute ICH. Acute blood pressure reduction is implemented only occasionally because of the poor evidence base for it, despite European and North American guidelines generally recommending antihypertensive treatment if systolic blood pressure exceeds 180mmHg.

Therefore, this year's publication of the second INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT 2) was a milestone in ICH research, because of its findings and its recruitment of 2,839 participants which was the largest sample size of any ICH trial to date. INTERACT2 was an international, multicentre, prospective, randomised, open-treatment, blinded end-point trial. In participants enrolled within six hours of ICH onset and a systolic BP 150-220mmHg, it compared the effects of BP targets of <140mmHg and <180mmHg on the primary outcome of death or major disability (modified Rankin scale 3-6) at 90 days. Allocation concealment was good. There were no baseline imbalances. There did not appear to be any imbalances between the two arms of the trial that could have confounded the findings (in particular, the frequency of ITU admission was similar between the two groups and if anything 'not for resuscitation' orders were more common in the intensive BP target group). Outcome assessment was not only complete (>98%) but also blind to allocated treatment.

INTERACT2 found that a systolic BP target of <140mmHg might be superior to <180mmHg on the primary outcome (odds ratio with intensive treatment, 0.87; 95% confidence interval [CI], 0.75 to 1.01; p=0.06). However, the intensive BP target seemed superior on a secondary, ordinal analysis of the primary outcome (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; p=0.04), which was added to the statistical analysis plan while the trial was ongoing but before the investigators were unblinded to the final dataset. The absolute risk reduction of 3.6% (number needed to treat=28) was in participants' dependence alone, because there was no difference in death between the two groups (see slide number 11 at http://www.interact2.org/wp-content/uploads/2013/05/RCT-session_INTERACT2_London_20131.pptx). There was no difference in major safety events, including neurological deterioration, between the groups indicating that intensive BP lowering, did not cause harm.

The results appear generalisable, although two thirds of participants were recruited in China. In China, urapidil is used for BP reduction, rather than labetalol, GTN, or nicardipine (which tend to be used in Europe and North America), although different drugs seem unlikely to differ in their effect on outcome. Crucially, the Chinese sub-group showed no interaction with treatment effect, and nor did time to randomisation, baseline BP, history of hypertension, or ICH characteristics.

The interpretation of INTERACT2 is challenging. Puritans may argue that the pre-specified primary outcome did not reach statistical significance and that acute BP reduction had small effects and still only seemed superior (risk reduction in death or dependence 3%, 95% CI 0 to 6; p=0.08) in a meta-analysis of the three randomised trials of acute ICH (INTERACT1, INTERACT2, and ATACH1). On the other hand, the secondary analysis is the most appropriate (because BP reduction is likely work across the range of stroke severities, not just at the dichotomy between dependence and independence), had the investigators compared a systolic BP target of <140mmHg to standard practice they might have found a larger effect, and finally BP reduction can be achieved cheaply if HDU/ITU admission is unnecessary and it appears safe in this context.

Overall, INTERACT2 is welcome news for a condition with so few treatment options. Although we are puritanical in our education and thinking we are also pragmatic in our hearts, so on balance we are sufficiently convinced to implement this intervention in our everyday practice. Who knows, ICH may have two acute treatments if the antifibrinolytic drug tranexamic acid proves to be beneficial, so UK neurologists are encouraged to support the ongoing TICH2 trial (www.tich-2.org).

PAPER OF THE YEAR: STROKE

Chosen article: ***Broderick JP, Palesch YY, Demchuk AM et al. Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke. N Engl J Med 2013; 368:893-903***

Reviewer: Prof Keith W Muir, SINAPSE Professor of Clinical Imaging & Consultant Neurologist, Institute of Neuroscience and Psychology, University of Glasgow, Scotland.

IA thrombectomy: Evaluation of innovation

Reperfusing the ischaemic brain is a logical treatment approach, and intravenous thrombolysis with the recombinant tissue plasminogen activator (rtPA) alteplase (our only proven acute treatment) significantly increases the chance of regaining independence. However, IV alteplase recanalises the occluded artery in only around 50-60% of patients, and is least effective in those with the largest clots (and therefore the most severe strokes). Intra-arterial (IA) devices that can disrupt or remove thrombus offer more effective recanalisation.

The Third Interventional Management of Stroke trial (IMS-3) was the latest in a series of academic trials evaluating IA therapy, dating back to the late 1990s, pursued tenaciously by

the stroke team at the University of Cincinnati and their collaborators. IMS-3 randomised acute ischaemic stroke patients to IV thrombolysis alone, or IV rtPA and IA device.

Regulatory systems in both North America and Europe approve devices on the basis that they do what they say - in this case, remove clot from an artery - and do not require evidence of clinical benefit. Despite no randomised controlled trials (RCTs) supporting clinical efficacy, healthcare systems in several countries offered generous reimbursement for IA thrombectomy using approved devices, fuelling a large number of procedures (>7000 per annum in the USA alone). Regrettably, academic rigor was a lower priority than healthy hospital finances, and IMS-3 took almost 6 years to achieve two-thirds of its planned recruitment, ultimately being terminated on grounds of futility – the data review committee concluded that there was no chance of seeing a significant difference between treatment arms - with 656 participants included.

This premature stop for futility was in itself a surprise for IA thrombectomy enthusiasts; a treatment so self-evidently "better" that randomisation was deemed unacceptable or unethical, clearly had an effect size much less than expected. IMS-3 found no difference between treatment arms for primary and secondary end-points, and also any pre-defined subgroup, despite superior recanalisation rates for IA treatment.

Trials of interventional procedures are always criticised on the grounds that the devices are not state of the art, the operators are inadequately experienced, and patient selection has been poor, and the duration of IMS-3 inevitably meant that older devices and selection techniques predominated (stent-retrievers and CTA angiography being late evolutions during the trial). However, participating centres were all well-organised, motivated and experienced, and IA thrombectomy was done according to best practice at the time. Despite this, the mean onset-to-procedure start time was 249 minutes. For a condition with such steep decline of benefit with longer onset-to-treatment time (as observed in the IV rtPA trials), this means that effect size in a trial will be small: in real life, this sobering figure from some of the best centres worldwide suggests that many procedures are unlikely to benefit patients.

There is a feeling of déjà vu, even for the déjà vu: IMS-3 emphasises once again that RCT level evidence should underpin adoption of new treatments, even more so when procedures are expensive, invasive and require major service reorganisation to deliver. But we have been here before, with EC-IC bypass, carotid endarterectomy, and stenting for both carotids and intracranial vessels, all self-evidently a good idea, all either ineffective or effective only in specific sub-groups after RCTs. IMS-3 has catalysed a large number of academic and commercial trials that will in the years ahead investigate whether there is a role for IA treatment for stroke, and if so for whom. Perhaps stent-retrievers, CTA selection, and earlier and faster intervention will be the key. It has highlighted also that healthcare and regulatory systems may still inadvertently conspire to trigger widespread adoption of innovations without proper evaluation. The contrasting experience of the MR CLEAN trial in the Netherlands, where IA treatment was not permitted except in the context of an RCT, is a salutary one.