

Brain protein key to identifying high risk concussion

Research carried out by a team from the University of Glasgow and University of Pennsylvania has identified the source of a brain protein linked with serious concussion symptoms (Johnson et al, 2015).

Concussion is the major medical issue currently facing sport. Defined as a 'mild' traumatic brain injury, the signs and symptoms of concussion are often subtle, making diagnosis difficult. In addition, although most athletes will recover within a week or so, a

proportion will have lingering symptoms which can last many months, including memory problems.

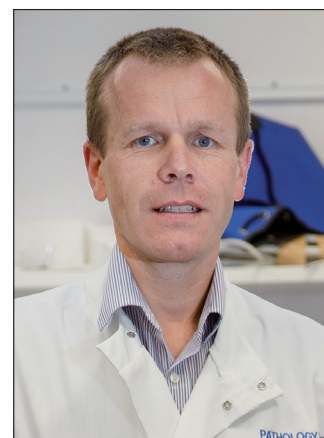
The challenges facing sport and medicine, therefore, are to find a way to make a confident diagnosis of brain injury and to identify those athletes who might be at risk of lasting symptoms.

The University of Pennsylvania team had previously identified that high blood levels of a brain protein known as alpha II-spectrin N-terminal

fragment, or SNTF, in patients with concussion could identify those with greater problems in recovery.

This latest research found that SNTF is created in damaged nerve fibres deep in the brain, a pathology known as diffuse axonal injury and that was effectively 'invisible' to standard brain scans and investigations in patients with concussion, until now.

Supporting its use as a biomarker of diffuse axonal injury, SNTF immunoreactive



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axons were observed at all time points following both human severe traumatic brain injury and in a model of mild traumatic brain injury. Interestingly, SNTF revealed a subpopulation of degenerating axons which were undetected by amyloid precursor protein, the gold-standard marker of transport interruption.

The new data support the idea that a blood test for SNTF could be developed to detect diffuse axonal injury in injured athletes. This could allow doctors to diagnose concussion and to predict those patients who might have prolonged symptoms.

Dr Stewart said: 'This represents a major step forward towards developing a biologically plausible blood test that could be used to detect concussion and direct injury management.'

Johnson VE, Stewart W, Weber MT, Cullen DK, Siman R, Smith DH (2015) SNTF immunostaining reveals previously undetected axonal pathology in traumatic brain injury. *Acta Neuropathol* (Epub ahead of print) (doi: 10.1007/s00401-015-1506-0)

Colorectal cancer classified into four distinct diseases with different diagnoses

An international study consortium has analysed and interpreted data on the diversity of colorectal cancers from different patients, to facilitate clinical translation of the knowledge about the different types of colorectal cancers (Guinney et al, 2015).

The consortium coupled clinical data with laboratory data and modern genomics data from more than 4000 patients in order to reach an agreement on how to understand and consolidate previously published molecular classifications of the disease.

The consortium agreed on one system with four groups or subtypes into which nearly all tumours could be classified, so-called consensus molecular subtypes. The criterion used to distinguish the subtypes is the set of most active genes that dictate the behaviour of each tumour and not the type of bowel tissue it affects or any other traditional criterion used in pathology.

Tumours of the same subtype are likely to react in similar ways to a given treatment, while tumours of different subtypes might react very differently. In other words, the treatment given to a patient should be optimized by knowing the tumour subtype.

The four subtypes are:

- CMS1 (microsatellite instability immune, 14%), hypermutated, microsatellite unstable and strong immune activation
- CMS2 (canonical, 37%), epithelial, marked WNT and MYC signalling activation
- CMS3 (metabolic, 13%), epithelial and evident metabolic dysregulation
- CMS4 (mesenchymal, 23%), prominent transforming growth factor- β activation, stromal invasion and angiogenesis.

Commenting on this work, one of the authors, Dr Mauro Delorenzi, Group Leader at SIB Swiss Institute of

Bioinformatics and at the University Lausanne Ludwig Cancer Center, said: 'This new classification could help achieve better outcomes. The CMS-1 tumours for example might be the most responsive to immunotherapies and patients might get high benefit from this kind of treatment. The CMS-4 tumours are the most aggressive ones and the patient might benefit from a more intense treatment, and one that combats their specific aggressive features.'

He summed up by saying: 'Each subtype requires a specific treatment plan and these should be developed in the next phase of research'.

The results give hope that this classification might lead to a more efficient treatment of bowel cancer and improve the current survival rates.

Guinney J, Dienstmann R, Wang X et al (2015) The consensus molecular subtypes of colorectal cancer. *Nature Med* **21**: 1350–6 (doi: 10.1038/nm.3967)

Effect of anti-VEGF treatment for diabetic macular oedema

Post-hoc analysis of best corrected visual acuity data in diabetic macular oedema patients treated with anti-vascular endothelial growth factor (anti-VEGF) therapy suggests that long-term response can be assessed after three injections, allowing other options to be used if no response is seen.

Antiepileptic drugs may progressively impair balance

In a study of 26 twin and sibling pairs where one of each pair had received long-term antiepileptic drug therapy, participants who were taking these medications swayed more during static and dynamic balance tests than their siblings who were not taking antiepileptic medications (doi: 10.1111/epi.13136).

Predicting risk of blindness and lower limb amputation in patients with diabetes

New algorithms calculate the absolute risk of developing blindness and requiring amputation over a 10-year period in patients with diabetes, taking account of their individual risk factors (doi: 10.1136/bmj.h5441).

Modified Valsalva manoeuvre improves cardioversion of supraventricular tachycardia

A randomized controlled, parallel-group trial was carried out at emergency departments in England to assess whether modification of the Valsalva manoeuvre would improve outcomes for patients with supraventricular tachycardia (Appelboam et al, 2015).

Adults presenting with supraventricular tachycardia (excluding atrial fibrillation and flutter) were randomly allocated in a 1:1 ratio to undergo a modified Valsalva manoeuvre (done semi-recumbent with supine repositioning and passive leg raise immediately after the Valsalva strain), or a standard semi-

recumbent Valsalva manoeuvre. A 40 mmHg pressure, 15 s standardized strain was used in both groups. The primary outcome was return to sinus rhythm at 1 minute after intervention.

A total of 433 participants were enrolled to the trial between January 2013 and December 2014, and 214 participants in each group were included in the intention-to-treat analysis.

Of 214 participants assigned to standard Valsalva manoeuvre 37 (17%) achieved sinus rhythm compared with 93 (43%) of 214 in the modified Valsalva manoeuvre group

(adjusted odds ratio 3.7, 95% confidence interval = 2.3–5.8; $P < 0.0001$). No serious adverse events were recorded.

This simple, cost-free, well-tolerated postural modification to the standard Valsalva manoeuvre is highly effective and substantially reduced the number of patients needing other emergency treatments, particularly adenosine.

Appelboam A, Reuben A, Mann C et al; REVERT trial collaborators (2015) Postural modification to the standard Valsalva manoeuvre for emergency treatment of supraventricular tachycardias (REVERT): a randomised controlled trial. *Lancet* **386**(10005): 1747–53 (doi: 10.1016/S0140-6736(15)61485-4)

Risk of infant death linked to maternal weight

Achieving a healthy weight before becoming pregnant and gaining an appropriate amount of weight during pregnancy significantly reduce the risk of the baby dying in the first year of life (Bodnar et al, 2015).

Every year, approximately 24 000 infants die in their first year of life in the United States. Dr Lisa Bodnar, associate professor in Pitt Public Health's Department of

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Epidemiology, and her colleagues examined records from more than 1.2 million births that occurred from 2003 to 2011 in Pennsylvania, including 5530 infant deaths (defined as the death of an infant before his or her first birthday).

The mothers were classified as underweight, normal weight, overweight or obese, which was divided into three grades based on their pre-pregnancy body mass index. In each group, the researchers also examined the impact on infant mortality when women gained significantly more or less weight during pregnancy than recommended by Institute of Medicine guidelines.

In all weight classes except the most obese, gaining less than or much more than recommended increased the risk of infant death. However, even when obese women gained the optimal weight during preg-

nancy, their risk of infant death was still about twice as great as that of women who began pregnancy at a normal weight.

'We are hopeful that this study can be used to start a dialogue between physicians and women on the importance of not only gaining a healthy amount of weight while pregnant, but also reducing excess weight before they become pregnant as a potential way to improve infant survival,' said Dr Bodnar.

The findings highlight the need for a comprehensive approach to obesity reduction among women of reproductive age which includes weight counselling before conception and during pregnancy.

Bodnar LM, Siminerio LL, Himes KP, Hutcheon JA, Lash TL, Parisi SM, Abrams B (2015) Maternal obesity and gestational weight gain are risk factors for infant death. *Obesity* (doi: 10.1002/oby.21335)

Sleep-disordered breathing predicts development of atrial fibrillation in older men

Sleep-disordered breathing often predicts the development of atrial fibrillation in older men, according to American researchers (May et al, 2015).

The researchers studied 842 men who were enrolled in the multicentre Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study). The average age of the men at enrollment was 75 years. Men with baseline atrial fibrillation were

Dr Reena Mehra, Director, Sleep Disorders Research, Cleveland Clinic, Cleveland, Ohio



excluded from further study. After an initial polysomnography test, they were followed for an average of 6.5 years. On follow-up, 99 patients had developed atrial fibrillation.

The following results were statistically significant: those with central sleep apnoea were 2.58 times more likely to develop atrial fibrillation than those without, those with central sleep apnoea-Cheyne Stokes respiration were 2.27 times more likely to develop atrial fibrillation than those without and those enrolled at age 76 years and older with obstructive sleep apnoea had a 22% increase in incident atrial fibrillation with each 5-unit increase in the apnoea-hypopnoea index.

The researchers did not find a significant association between study participants with obstructive sleep apnoea and atrial fibrillation.

Obstructive sleep apnoea is the most common type of sleep-disordered breathing. In the subset of patients 76 years of age and older, however, obstructive sleep apnoea did predict atrial fibrillation, according to the researchers.

'Gaining insight into the role that sleep-disordered breathing plays in atrial fibrillation may help researchers and clinicians develop targeted therapies that address the physiological determinants of abnormal sleep-related breathing leading to atrial fibrillation,' said senior investigator Dr Reena Mehra, director of sleep disorders research, at the Cleveland Clinic.

May AM, Blackwell T, Stone PH et al, for the Osteoporotic Fractures in Men (MrOS) Study Group (2015) Central sleep disordered breathing predicts incident atrial fibrillation in older males. *Am J Respir Crit Care Med* (doi: 10.1164/rccm.201508-1523OC)

Platelets promote liver regeneration after surgery

A team of researchers has discovered that certain platelet-derived growth factors are of major significance for the liver's regeneration processes (Starlinger et al, 2015). Platelets can encourage the regrowth of liver tissue in patients who have had parts of their liver removed surgically. This may also act as a starting point for the prediction of potential postoperative problems.

Platelets can specifically secrete key growth factors at the site of the injury and therefore start the regeneration process. In this collaboration between the University Department of Surgery and the Institute of Physiology at the MedUni Vienna, scientists demonstrated that the specific release of growth factors from the α granules was associated with postoperative liver regeneration.

The researchers concluded that the postoperative profile of circulating platelet-derived factors correlates with the ability of the remnant liver to regenerate. Selective modulation of platelet α -granule release in patients may be an attractive target for therapeutic interventions to improve liver regeneration and clinical outcomes after partial hepatectomy.

Starlinger P, Haegele S, Offensperger F et al (2015) The profile of platelet α -granule released molecules affects postoperative liver regeneration. *Hepatology* (doi: 10.1002/hep.28331)

Opioid addiction in over half of female methadone patients originates from prescribed painkillers

Painkillers prescribed by doctors are the starting point for addiction to opioids for more people than heroin, according to a study of 503 patients attending methadone clinics (Bawor et al, 2015). The study highlights the differences in profile of those who currently seek treatment and people that treatment plans were originally designed for.

The results show that over half (52%) of women and over a third (38%) of men reported doctor-prescribed painkillers as being their first contact with opioid drugs.

Researchers from McMaster University in Canada recruited men and women from 13 methadone clinics in Ontario, Canada. The participants were attending the clinics for opioid dependence disorder, and provided researchers with detailed information on their health and lifestyle, as well as urine tests for drug use.

The study aimed to identify any significant gender differences between men and women attending the clinics. Women had more physical and psychological health problems, more childcare responsibilities, and

were more likely to have a family history of psychiatric illness than men. Men were more likely to be in employment, and more likely to smoke cigarettes. Rates of cannabis use were relatively high among men and women, with nearly half (47%) of participants self-reporting use of the drug in the month before the study.

Bawor M, Dennis BB, Varenbut M et al (2015) Sex differences in substance use, health, and social functioning among opioid users receiving methadone treatment: a multicentre cohort study. *Biol Sex Differ* 6: 21 (doi: 10.1186/s13293-015-0038-6)

Withdrawing donepezil doubles risk of patients with Alzheimer's disease moving to a nursing home

Withdrawing donepezil from people in the advanced stages of Alzheimer's disease doubles their risk of moving to a nursing home within a year (Howard et al, 2015).

Researchers at University College London monitored 295 people with moderate to severe Alzheimer's disease to

see the effects of continuing or discontinuing the drug donepezil – which is typically withdrawn in the later stages of the disease because of a lack of perceived benefit by clinicians.

The participants were randomly selected to either continue donepezil or withdraw

from the drug by receiving a placebo. These two groups were then each divided to test the effect of receiving memantine or a placebo.

The trial found that withdrawing donepezil doubled the risk of moving the patient to a nursing home after a year. Memantine was not found to have any effect on the risk of moving to a nursing home.

In the UK, 70% of care home residents have dementia or severe memory problems. The average cost of residential care for people with dementia is estimated to be between £30732 and £34424 per year. By comparison, donepezil costs £21.59 per year.

Professor Robert Howard, Professor of Old Age Psychiatry at University College London, said: 'Continuing with donepezil treatment provided modest benefits in cognitive function and in how well people could perform their daily activities... We are all impatient for the advent of true disease-modifying drugs that can slow or halt the Alzheimer process, but donepezil is available right now and at modest cost.'

Howard R, McShane R, Lindsay J et al (2015) Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. *Lancet Neurol* 14(12): 1171–81 (doi: 10.1016/S1474-4422(15)00258-6)

Female reproductive factors linked to risk of death

Reproductive factors in women, such as a later starting age of menstruation, having children and breastfeeding, are associated with a reduced risk of death (Merritt et al, 2015). A better understanding of how these influence long-term health could help develop clinical strategies to improve women's health.

Researchers analysed data from 322 972 women from 10 countries that participated in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. At the start of the study, participants completed questionnaires and interviews about diet, lifestyle characteristics and medical history to capture baseline characteristics. Each woman was followed for an average of 12.9 years. There were 14 383 deaths overall, including 5938 from cancer and 2404 from circulatory system diseases.

Women who gave birth early (aged 20 years or less) or later in life (aged 31 years or more) had a higher risk of death than those who gave birth aged 26–30 years old. As this study was observational it

was not possible to conclude that these factors were the reason that risk was reduced.

Lead author, Dr Melissa Merritt from Imperial College London, said: 'Several reproductive factors were associated with a significantly lower risk of death. Many of these associations were also apparent when we considered cause-specific deaths from total cancer and ischaemic heart disease.'

Merritt MA, Riboli E, Murphy N et al (2015) Reproductive factors and risk of mortality in the European Prospective Investigation into Cancer and Nutrition: a cohort study. *BMC Med* 13: 252 (doi: 10.1186/s12916-015-0484-3)

Dr Melissa Merritt, Research Fellow in Cancer Epidemiology, Faculty of Medicine, School of Public Health, Imperial College London



Mental Health under pressure highlights need for stability

A new briefing from the King's Fund (Gilbert, 2015) looks at mental health services for adults between the ages of 16 and 65 years. The briefing highlights that the absence of robust data makes it difficult to definitively assess the state of mental health services. What is clear is that it is a sector under huge pressure. While increased political support and a stronger policy focus is welcome, parity of esteem for mental health remains a long way off.

The briefing also emphasizes that as their financial position deteriorates, many mental health trusts are considering another wave of large-scale changes. This risks destabilizing services further and reducing the quality of care for patients.

Mental health services must focus on using evidence to improve practice and reduce variations in care, but this must be underpinned by stable funding.

Responding to the briefing, Stephen Dalton, Chief Executive of the Mental Health Network, said: 'Many commissioners of NHS services don't have the capacity to do the right thing and fund what works. If this government is serious about prioritizing mental health they need to ensure new funding gets directly to providers of care and not channelled through layers of bureaucracy where it is lost.'

Gilbert H (2015) Mental health under pressure. www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/mental-health-under-pressure-nov15_0.pdf (accessed 24 November 2015)