Institution:
University of Cambridge

Unit of Assessment:
UoA4

Title of case study:
Management and outcome of head injury and cerebrospinal fluid disorders: from experimental medicine to standard clinical practice

1. Summary of the impact (indicative maximum 100 words)

Novel methods of measurement developed by Marek Czosnyka, Peter Hutchinson, David Menon and John Pickard have provided new insights into the pathophysiology of brain injury, led to commercial applications, and influenced patient care in terms of improved outcome for clinical trials. Multimodality brain monitoring of intracranial pressure (ICP), brain oxygen and microdialysis; PET/MRI imaging of critically ill patients; and computerised CSF infusion tests for shunt function in hydrocephalus have each impacted on the clinical practice and the ability to evaluate novel treatments and interventions in brain injury. This work has led directly to the establishment of a National Institute for Health Research (NIHR) Health Technology Cooperative for Brain Injury.

2. Underpinning research (indicative maximum 500 words)

In 1991 a research group was established across Departments in the Cambridge University Clinical School to undertake research in traumatic brain injury (TBI) and abnormalities of CSF. The group was led jointly by Marek Czosnyka (Senior Research Associate, 1991; Professor of Brain Physics, from 2013), Peter Hutchinson (Reader in Neurosurgery, 2008-date; NIHR Professor from 2013), David Menon (University Lecturer, 1993; Professor of Anaesthesia, from 2000) and John Pickard (Professor of Neurosurgery, from 1991). Central to the impact has been the introduction of technologies derived from brain physics for real-time measurement of brain function in the context of acute injury. Technology that combines monitoring and imaging techniques has been licensed and has increased understanding of the pathophysiology of TBI and CSF disorders; defined optimal physiological parameters associated with best outcome in clinical trials; and altered the care of patients in the neurosciences intensive care setting nationally and internationally. The research encompasses four domains:

Brain physics: By applying multimodal brain monitoring[1] (introduced 1991**)** novel indices of cerebrovascular physiology have been defined including autoregulation with the following major findings:

- TBI: (1) cerebrovascular pressure reactivity independently associates with outcome; (2) extremes of cerebral perfusion pressure (CPP) contribute to worse outcome; and (3) optimal CPP is a valid therapeutic target (2012)[2]
- CSF: (1) non-invasive ICP can be estimated from cerebral blood flow velocity and arterial pressure (2000); (2) normal pressure hydrocephalus results from a dysfunction of CSF dynamics, white matter softening and dysautoregulation with aging (2008); and (3) idiopathic intracranial hypertension can be treated with venous stenting (2002)[3]

Neurochemistry: Cerebral microdialysis (introduced 1997) is applied to monitor cerebral metabolism in TBI demonstrating that:

- brain microdialysate chemistry in TBI patients relates to clinical outcome (notably the lactate/ /pyruvate ratio: 2011)
- cerebral metabolism in TBI patients studied by ^{13}C-labelled microdialysis indicates that lactate can act as a cerebral energy substrate (first direct demonstration in the human brain: 2009)[4]
- TBI is associated with a sequential production of cytokines (2012).

Neuroimaging: The application of MRI and PET to patients in the Wolfson Brain Imaging Centre (founded 1997) adjacent to the Neurocritical Care Unit has defined regional and global derangements of brain structure and function following TBI: specifically, mapping of cerebral blood flow, oxygenation using PET, and tractography with advanced MRI. Findings include:

- mapping regional oxygenation and defining the impact of a therapeutic manoeuvre (hyperoxia) after TBI (2008)[5]

- imaging traumatic axonal injury with diffusion tensor imaging and relating injury to outcome (2011)
- mapping amyloid deposition after TBI using [^{11}C] PIB PET (2013).

Clinical trials: The multicentre international randomised international trial of decompressive craniectomy (RESCUEicp) for the management of refractory TBI has been led by the group (results due 2014); and the management of chronic subdural haematoma has been changed worldwide by the findings of randomized study of chronic subdural haematoma also led by the group (2009).[6]

3. References to the research (indicative maximum of six references)

1. Czosnyka M, Whitehouse H, Smielewski P, Kirkpatrick P, Guazzo EP, Pickard JD, 1994. Computer supported multimodal bed-side monitoring for neuro intensive care. Int J Clin Monit Comput 11: 223-32

2. Aries MJ, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, Hutchinson PJ, Brady KM, Menon DK, Pickard JD, Smielewski P, 2012. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med 40: 2456-63

3. Higgins JN, Owler BK, Cousins C, Pickard JD, 2002. Venous sinus stenting for refractory benign intracranial hypertension. Lancet 359: 228-30

4. Gallagher CN, Carpenter KLH, Grice P, Howe D, Mason A, Timofeev I, Menon DK, Kirkpatrick PJ, Pickard JD, Sutherland G, Hutchinson PJ, 2009. The human brain utilizes lactate via the tricarboxylic acid cycle: a ^{13}C-labelled microdialysis and high-resolution nuclear magnetic resonance study. Brain 132: 2839-2849

5. Nortje J, Coles JP, Timofeev I, Fryer TD, Aigbirhio FI, Smielewski P, Outtrim JG, Chatfield DA, Pickard JD, Hutchinson PJ, Gupta AK, Menon DK, 2008 Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: preliminary findings. Crit Care Med 36: 273-81

6. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, Richards HK, Marcus H, Parker RA, Price SJ, Kirollos RW, Pickard JD, Hutchinson PJ, 2009. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. Lancet 374: 1067-73

Grant support
The research program has been funded by a series of grants from the MRC, Wellcome Trust, NIHR, Academy of Medical Sciences / Health Foundation and EU. Total grant income over the research period 1993-2013 has exceeded £10M. In April 2013 as part of a consortium we have been awarded a EU Grant Collaborative European NeuroTrauma Effectiveness Research in TBI (co-leads David Menon [Cambridge] and Andrew Maas [Antwerp]; up to €29.9M for a period of up to 78 months).

4. Details of the impact (indicative maximum 750 words)

The research has made a major contribution to the management of patients with TBI and CSF disorders in terms of scientific, clinical and social impact. Contribution to the health of the nation and beyond have been demonstrated by improvement in outcome for patients with TBI and CSF disorders. The findings (>100 Medline publications) have resulted in changes in policy, practice and in public understanding. Specifically this work has resulted in the establishment of protocols and networks for the management of ITU patients, contributions to the NICE guidelines for head injury[1] (David Menon and Peter Hutchinson Guideline Development Group members 2013) and CSF disorders (2008)[2] , and leadership in setting up Neurocritical Care (NCCnet founded 2007), and Neurosurgical[3] (British Neurotrauma Group[4] founded 2010, International Society for Hydrocephalus and CSF Disorders founded 2008) Networks. In 2013 we have established a

National Institute for Health Research (NIHR) Health Technology Cooperative for Brain Injury[5]. The achievements are:

1 Novel treatment strategies

(a) **Protocol driven therapy in TBI.** A rational physiological basis for therapy targets: specifically optimal strategies for control of ICP have been defined. The potential use of hyperoxia has been explored. These targets have been incorporated within our management protocols (established in 1997 with subsequent revisions) and adopted by several centres nationally and internationally. The implementation of protocol driven therapy has resulted in continued improvements in outcome from head injury since 1997, up to the present day. The latest data (2013) from the Trauma and Audit Research Network shows Cambridge achieving excellent performance (in excess of two standard deviations expected) of adjusted measures of outcome.[6]

(b) **Venous stenting in Idiopathic Intracranial Hypertension.** This concept was first described by us worldwide (2000) and over 200 patients have now been stented. Our technique has been taken up internationally and for an expanding range of indications in Cambridge including tinnitus, intrasinus meningiomas and complex extracranial venous disorders in patients who have sometimes been dismissed as undiagnosable or with functional illnesses. Currently approximately 40 stents per annum are performed in Cambridge and the technique has been taken up in North America, France, Italy and Australia (>100 performed).

(c) **Clinical trials and registries.** The following have been led by us:

- an international RCT of decompressive craniectomy in TBI (RESCUEicp) (385/400 patients recruited to 2013)[7]
- a RCT of the use of drains following evacuation of chronic subdural haematoma showing reduction in recurrence and mortality (215 patients- completed 2009)
- a RCT of silver impregnated external ventricular drainage catheters to reduce infection (325 patients- completed 2012)
- STASH, a multicentre RCT of Simvastatin in aneurysmal subarachnoid haemorrhage (803 patients- recruitment completed 2013)
- formation of the ORION platform (2012) for national clinical registries including the UK shunt registry, acoustic schwannoma and paediatric epilepsy surgery.

2 Advances in clinical monitoring and imaging: Monitoring of cerebral physiology and chemistry and imaging of ventilated TBI patients has been developed. The use of cerebrovascular pressure reactivity and calculation of optimal CPP to guide therapy was pioneered by us. Cambridge is one of the leading units worldwide in terms of applying PET and microdialysis to monitor brain metabolism in the injured brain. Major achievements have been to demonstrate the relationship between brain chemistry and outcome, demonstration that lactate may be used as a substrate in the injured brain (^{13}C technology) and definition of the inflammatory response to TBI. Microdialysis is now used in routine monitoring of patients with severe TBI.

3 Inventions: Specialised software for brain monitoring (ICM plus) developed by us (2004) is now used for advanced brain monitoring in neurosurgical centres for worldwide[8] (70 licences sold to date generating revenue of over £250K). The development and implementation of ICM+ software started in 2003 and has led to the creation of various international collaborations both academic and commercial (Moberg Ltd, USA, 2009; and Hemmodia [France], 2013).

A MRI compatible triple lumen cranial access device to transmit monitoring probes into the brain (invented 1997) and a computerised CSF infusion test (invented 1991) to assist in the diagnosis of various disorders of the CSF circulation have both been developed in Cambridge. The CSF infusion test is now used in Bristol, Leeds, the Hague, Tubingen, Toulouse and Geneva; and by checking shunt function without the need for surgery this has spared 30-50 patients from unnecessary surgery per year in Cambridge alone.

The creation of the UK Shunt Evaluation Laboratory (founded 1992) has enabled the evaluation of shunts providing information that is independent of the manufacturers. The UK Shunt Registry developed (1995) and hosted by us has provided unique long term follow up of 70,000 operations

in 35,000 patients in the UK and includes the epidemiology of different CSF disorders, and audit of the performance of individual neurosurgery units and shunt components. The ORION platform for cloud-based national registries was also created in Cambridge (Alexis Joannides, lecturer in neurosurgery) involving the UK shunt registry, paediatric epilepsy surgery and acoustic schwannoma).

4 Training: The research has had impact on training the next generation of academic clinicians in acute brain injury with a program of fellowships and lectureships including NIHR Academic Clinical Fellowships, Clinical lecturers, Academy of Medical Sciences / Health Foundation Clinician Scientists, MRC Clinical Training Fellowships and Royal College of Surgeons Research Fellowships. These staff now apply techniques developed in Cambridge in practice throughout many centres for neurosurgery in the UK and elsewhere. This is particularly important given concerns regarding the future of academic training in surgery, anaesthesia and intensive care. There has also been a major contribution to the training of the next generation of basic scientists interested in CSF and TBI.

5 Societal impact: Major contributions to two BBC television programs – *Between Life and Death* (2011) and Lifesavers,[9] a trauma documentary (2013) has increased public understanding of science in head injury. Collaboration both clinically and academically with 'Headway'[10] (the charity representing head-injured patients) and directly with patients has also raised public awareness (e.g. co-application with Wellcome Trust People's Award – Science Made Simple). Strategies for prevention (e.g. use of cycle helmets) have also been promoted.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults- http://www.nice.org.uk/CG56

2. Lumbar infusion test for the investigation of normal pressure hydrocephalus- http://www.nice.org.uk/IPG263

3. Mendelow AD, Timothy J, Steers AJW, Lecky F, Yates D, Bouamra O, Woodford M, Hutchinson PJ, 2008. Management of Patients with Head Injury: Lancet 23: 685-7

4. British Neurotrauma Group- http://www.ukneurotrauma.org.uk/

5. http://www.nihr.ac.uk/infrastructure/Pages/HTCs.aspx

6.The Trauma Audit and Research Network- www.tarn.ac.uk

7. Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-Cranial Pressure- www.RESCUEicp.com

8. ICM+ Brain Monitoring Software- http://www.neurosurg.cam.ac.uk/pages/ICM/about.php

9. BBC Lifesavers - http://www.bbc.co.uk/programmes/b02w4w7v

10. Headway- www.headway.org.uk/