Early outcome prediction after severe traumatic brain injury: can multimodal magnetic resonance imaging assist in clinical prognostication for individual patients?

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Traumatic brain injury — a huge problem for society

Traumatic brain injury (TBI) is a leading cause of mortality and long-term disability, particularly affecting young people. It has been called "a silent epidemic".[1] The Australasian Traumatic Brain Injury Study (ATBIS)[2] identified 485 patients admitted to intensive care units with moderate or severe TBI in Australia and New Zealand (ANZ) over a 6-month period. These individuals had a 27.4% mortality rate and a 50.6% "unfavourable" neurological outcome (severe disability or death) rate 6 months after the injury. The validity of these findings has been confirmed in ANZ among patients with TBI included in the Saline vs Albumin Fluid Evaluation (SAFE) trial.[3,4] Thus the mortality and long-term neurological morbidity associated with moderate and severe TBI in ANZ is devastatingly high.

Despite current best therapies, half the patients with moderate and severe TBI are never capable of living independently in the community, and a significant number of survivors require high-level nursing care for the rest of their lives. The human and financial costs of supporting these severe disability survivors are substantial, as the disabling effects of TBI persist for many years.[5-7] However, the ability to reliably predict long-term functional outcome early in the clinical course of severe TBI is difficult, and the development of accurate predictors has been an important but as yet relatively disappointing area of TBI research over the past three decades. Recently, clinical predictors derived from very large datasets have influenced predictive models such that they work reasonably well for groups, but are insufficient to guide clinical practice in individual patients.

Current clinical predictors of long-term outcome

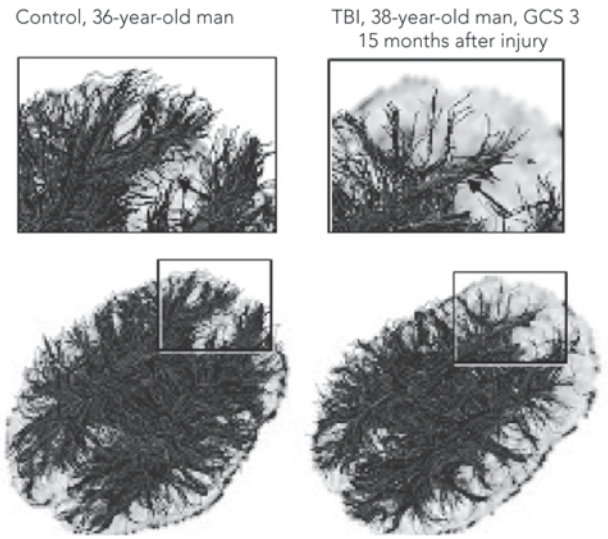
When patients with non-penetrating TBI present with a Glasgow Coma Scale (GCS) score of 3, fixed dilated pupils following prolonged periods of hypoxia and hypotension, and computed tomography (CT) evidence of cisternal collapse or herniation in the absence of a surgically evacuable lesion, clinicians generally feel comfortable prognosticating and guiding clinical management appropriately. However, this situation is the exception after severe TBI, and in the face of uncertainty, clinicians (backed by families) tend to err conservatively and continue aggressive management for many months in the hope of a favourable functional outcome. Sadly, meaningful recovery rarely occurs in the most severely injured patients. This raises ethical concerns about the appropriateness of applying aggressive therapy in all such cases.[5] Furthermore, this scenario is not only harrowing for patients and their extended family but also consumes enormous amounts of health care resources.

In an attempt to improve early prognostication and to direct aggressive therapy to patient cohorts who are more likely to benefit, researchers have studied a number of potential early predictive markers in TBI. To date, these have largely consisted of clinical assessment variables (GCS, duration of post-trauma amnesia); age; physiological variables (hypotension [systolic blood pressure < 90 mmHg], hypoxia [$PaO_2 < 60$ mmHg], abnormal papillary responses); biological markers (astroglial protein S100B, glial fibrillary acidic protein, serum neurone-specific enolase); and genetic markers (apolipoprotein E).[8-12] These markers have improved our predictive ability in groups of patients (see IMPACT prognostic calculator website [http://www.tbi-impact.org/?p=impact/calc]), but are not sufficiently precise to direct therapy decisions in individual patients.

Furthermore, efforts to find reliable prognostic markers have been hampered by the large variability in outcomes following TBI. This variability is likely accounted for by our current relatively crude severity grading system based on GCS (mild GCS 13–15, moderate GCS 9–12 and severe GCS ≤ 8), which results in an extremely heterogeneous group of structural injuries, with different clinical courses and outcomes being treated as a common entity. For example, traumatic axonal injury (TAI) and extradural haematoma may have equivalent GCS scores despite being entirely different types of injury. Thus there is considerable difficulty in using a severity grading based on a global clinical assessment marker that has no correlation with structural brain injury.

The ability to accurately identify, at an early stage (< 13 days into their clinical course), patients at risk of profound long-term severe disability after severe TBI would transform clinicians' approaches. Rational palliative care in appropriate patients would become an early treatment option for those identified with devastating outcomes. However, given the

Figure 1. Streamline tractography of the brain of a normal person compared with a survivor of severe traumatic brain injury (TBI)



Tractography is a 3D representation of DTI MRI that enables clear representation of ascending and descending white matter tracts. Here, the white matter tracts of normal brain are contrasted with those of a matched severe TBI survivor, where the anatomic deficits are clear. (Figure from Professor David Menon, Wolfson Brain Imaging Centre, University of Cambridge (UK), with permission.)

DTI = diffusion tensor imaging. GCS = Glasgow Coma Scale. MRI = magnetic resonance imaging.

high stakes in withdrawing care within this patient group, a highly specific and sensitive tool is required.

Can neuroimaging offer a new perspective?

Brain imaging by CT and standard magnetic resonance imaging (MRI) is invaluable for defining lesions that require immediate neurosurgical intervention. However, while CT evidence of cisternal compression, subarachnoid blood and midline shift/mass lesion and MRI evidence of deep injury (in the pons, medulla, or midbrain) are associated with a poor outcome, these tools currently lack the specificity to allow judgement on long-term functional outcome in most cases. This may in part be due to their insensitivity to detect more subtle white matter injuries, including TAI.

TAI, or diffuse axonal injury, is a very common and important injury after TBI,[13] and reflects damage to the tracts of white matter that connect vital structures of the brain. TAI, when identified, has been shown to be associated with significant disability and poor outcome, including the majority of TBI-related cognitive deficits.[14] TAI occurs when shearing forces act on neurones as the head is rapidly accelerated or decelerated, as frequently occurs in trauma. The resultant damage to the axons can be quantified histologically, but is poorly visualised by conventional in-vivo imaging methods,[14-17] and thus commonly missed. While indicators such as oedema may indicate axonal damage, in many cases the microscopic changes that occur cannot be picked up by conventional imaging techniques such as CT or structural MRI scans. A simple analogy is that the brain is like a computer and conventional imaging cannot detect any damage to the wiring between important structures. Thus, like a computer, the brain will not function if the wiring has been disrupted although all the key functional areas appear grossly structurally intact.

Recent advances in neuroimaging have identified MRI tools that may prove to be more sensitive and specific in identifying functional and microstructural changes that occur in TBI but are regularly missed with routine scanning. Thus such tools may potentially provide more accurate prediction of outcome.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a new modality of MRI scanning that offers much promise and has a significantly greater sensitivity for detecting white matter microstructural injuries in the brain of people with TBI (Figure 1). DTI is a sophisticated technique that examines both the directionality and magnitude of diffusion of water molecules in structures in the brain.[18-22] It is based on the principle of Brownian motion, the random thermally driven movement of molecules. In an ideal solution without barriers, this motion is equal in all directions (isotropic). However, where the molecules are restrained by physical barriers such as in a neurone, the motion tends to be greater along the axis of the neurone than across the breadth of the neurone (anisotropic). DTI utilises this property of neurones (brain white matter) to relate changes in anisotropy to the microarchitecture of the brain. This is important, as changes to the barriers of diffusion after injury such as TAI result in changes in the measured diffusion signal. Thus DTI may provide a more sensitive measure of white matter injury, including TAI.

Clinical studies of DTI in patients with TBI

In support of a clinical role of DTI in patients with TBI, studies have demonstrated that DTI has improved sensitivity to detect white matter lesions not previously found using conventional imaging techniques[23] and that it is superior at specifically detecting TAI.[24,25] Importantly this has been confirmed histologically in laboratory studies.[15,16] In addition, it has also been observed that TBI patients with unfavourable outcomes have deep grey and white matter

changes[26] and a greater number of brainstem lesions[27] detected by DTI. A number of studies have identified correlations between DTI measures and the severity and outcome after TBI,[28] with some currently predicting that DTI may outperform current clinical measures.[29-31] A longitudinal study conducted by Sidaros and colleagues examined 30 adult patients at about 8 weeks and 12 months after TBI.[32] They found a reduction in measures of anisotropy in TBI patients compared with healthy controls, and these DTI measures were useful in predicting dichotomised functional neurological outcome (extended Glasgow Outcome Scale) at 1 year. Other studies have suggested that DTI alone may have a sensitivity and specificity approaching 90% for determining functional outcome after severe TBI.[33]

Magnetic resonance spectroscopy

While DTI examines structural anatomy after injury, magnetic resonance spectroscopy (MRS) measures brain metabolism — in particular, the relative amounts of specific metabolites in brain tissue.[22] MRS equipment can be tuned (just like a radio receiver) to pick up signals from different chemical nuclei within the body. Common neurochemicals that are measured with proton MRS include *N*-acetylaspartate (NAA, a marker of neuronal health); creatinine (a marker of energy metabolism); choline (a constitutive component of cell membranes, assessing glial proliferation or membrane breakdown); and lactate (a marker of anaerobic metabolism and ischaemia).[34,35]

Clinical studies of MRS in patients with TBI

MRS-detected reductions in the NAA/creatinine ratio and increases in levels of glutamate/glutamine (Glx), choline and lactate have been reported in patients after TBI, and these findings have been correlated with a poorer prognosis.[22,36,37] One study showed that Glx levels and choline/NAA ratios predicted long-term outcome with 94% accuracy (4% false positive and 12% false negative) and, when combined with the motor GCS score, provided a 97% predictive accuracy (no false positive and 12% false negative).[37] Furthermore, a recent single-centre French study reported that combined DTI and MRS predicted an unfavourable outcome in severe TBI patients with 97% specificity.[38] This suggests that combining these two distinct neuroimaging techniques into a single assessment tool may provide a powerful early predictive measure in TBI.

Future directions and summary

While these preliminary findings suggest that DTI and MRS may have significant potential as prognostic biomarkers in TBI, it must be noted that studies to date have had significant limitations. These studies have been relatively small, single-centre studies; heterogeneous in their patient selection, severity of injury, and time of MRI assessment after TBI; and varied in their timing of outcome assessment and in the outcome assessment tool used.[22] Moreover, the correlation between lesions identified by DTI and histological changes will require ongoing validation and, as with all neuroimaging techniques, individual variation in human brain anatomy will continue to pose challenges in interpretation. Neuroimaging is a "sexy" branch of science producing alluring images that we are eager to interpret, but it is important not to be seduced by these complex techniques before they have been adequately validated in large multicentre clinical studies, especially when the stakes for our individual patients are so high.

However, these results are certainly promising, and future post-TBI studies of much greater numbers of patients may accurately determine the sensitivity and specificity of multimodal MRI prognostication in TBI and may reveal it to be a reliable early clinical decision-making tool for critical care clinicians and neurologists. In addition, multimodal MRI may be useful in future research studies to help define therapeutic windows for treating diffuse brain injury. This could potentially provide surrogate measures of outcome in future trials of therapies in TBI[39] and ultimately help to achieve even better outcomes.

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References

1 Goldstein M. Traumatic brain injury: a silent epidemic. *Ann Neurol* 1990; 27: 327.
2 Myburgh JA, Cooper DJ, Finfer SR, et al. Epidemiology and 12-month outcomes from traumatic brain injury in Australia and New Zealand. *J Trauma* 2008; 64: 854-62.
3 Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007; 357: 874-84.

4 Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350: 2247-56.

5 Jennett B. Thirty years of the vegetative state: clinical, ethical and legal problems. *Prog Brain Res* 2005; 150: 537-43.

6 Patel HC, Bouamra O, Woodford M, et al. Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational study. *Lancet* 2005; 366: 1538-44.

7 Access Economics for the Victorian Neurotrauma Initiative. The economic cost of spinal cord injury and traumatic brain injury in Australia. Melbourne: VNI, 2009. http://www.accesseconomics.com.au/publicationsreports/search.php?searchfor=spinal+cord+injury&from=0 (accessed Jan 2011).

8 Engberg A. Severe traumatic brain injury — epidemiology, external causes, prevention, and rehabilitation of mental and physical sequelae. *Acta Neurol Scand Suppl* 1995; 164: 1-151.

9 Greenwood R. Value of recording duration of post-traumatic amnesia. *Lancet* 1997; 349: 1041-2.

10 Hukkelhoven CW, Steyerberg EW, Rampen AJ, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *J Neurosurg* 2003; 99: 666-73.

11 Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993; 34: 216-22.

12 Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2007; 24 Suppl 1: S1-106.

13 Jennett B, Adams JH, Murray LS, Graham DI. Neuropathology in vegetative and severely disabled patients after head injury. *Neurology* 2001; 56: 486-90.

14 Inglese M, Makani S, Johnson G, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* 2005; 103: 298-303.

15 Mac Donald CL, Dikranian K, Song SK, et al. Detection of traumatic axonal injury with diffusion tensor imaging in a mouse model of traumatic brain injury. *Exp Neurol* 2007; 205: 116-31.

16 Mac Donald CL, Dikranian K, Bayly P, et al. Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *J Neurosci* 2007; 27: 11869-76.

17 Mittl RL, Grossman RI, Hiehle JF, et al. Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. *AJNR Am J Neuroradiol* 1994; 15: 1583-9.

18 Sotak CH. The role of diffusion tensor imaging in the evaluation of ischemic brain injury — a review. *NMR Biomed* 2002; 15: 561-9.

19 Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. *J Head Trauma Rehabil* 2010; 25: 241-55.

20 Mascalchi M, Filippi M, Floris R, et al. Diffusion-weighted MR of the brain: methodology and clinical application. *Radiol Med* 2005; 109: 155-97.

21 Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics* 2007; 4: 316-29.

22 Weiss N, Galanaud D, Carpentier A, et al. Clinical review: prognostic value of magnetic resonance imaging in acute brain injury and coma. *Crit Care* 2007; 11: 230.

23 Xu J, Rasmussen IA, Lagopoulos J, Haberg A. Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *J Neurotrauma* 2007; 24: 753-65.

24 Liu AY, Maldjian JA, Bagley LJ, et al. Traumatic brain injury: diffusion-weighted MR imaging findings. *AJNR Am J Neuroradiol* 1999; 20: 1636-41.

25 Huisman TA, Sorensen AG, Hergan K, et al. Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. *J Comput Assist Tomogr* 2003; 27: 5-11.

26 Hou DJ, Tong KA, Ashwal S, et al. Diffusion-weighted magnetic resonance imaging improves outcome prediction in adult traumatic brain injury. *J Neurotrauma* 2007; 24: 1558-69.

27 Ezaki Y, Tsutsumi K, Morikawa M, Nagata I. Role of diffusion-weighted magnetic resonance imaging in diffuse axonal injury. *Acta Radiol* 2006; 47: 733-40.

28 Salmond CH, Menon DK, Chatfield DA, et al. Diffusion tensor imaging in chronic head injury survivors: correlations with learning and memory indices. *Neuroimage* 2006; 29: 117-24.

29 Huisman TA, Schwamm LH, Schaefer PW, et al. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *AJNR Am J Neuroradiol* 2004; 25: 370-6.

30 Ptak T, Sheridan RL, Rhea JT, et al. Cerebral fractional anisotropy score in trauma patients: a new indicator of white matter injury after trauma. *AJR Am J Roentgenol* 2003; 181: 1401-7.

31 Benson RR, Meda SA, Vasudevan S, et al. Global white matter analysis of diffusion tensor images is predictive of injury severity in traumatic brain injury. *J Neurotrauma* 2007; 24: 446-59.

32 Sidaros A, Engberg AW, Sidaros K, et al. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 2008; 131: 559-72.

33 Perlbarg V, Puybasset L, Tollard E, et al. Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: a diffusion tensor imaging study using voxel-based approaches. *Hum Brain Mapp* 2009; 30: 3924-33.

34 Garnett MR, Cadoux-Hudson TA, Styles P. How useful is magnetic resonance imaging in predicting severity and outcome in traumatic brain injury? *Curr Opin Neurol* 2001; 14: 753-7.

35 Brooks WM, Friedman SD, Gasparovic C. Magnetic resonance spectroscopy in traumatic brain injury. *J Head Trauma Rehabil* 2001; 16: 149-64.

36 Sinson G, Bagley LJ, Cecil KM, et al. Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: correlation with clinical outcome after traumatic brain injury. *AJNR Am J Neuroradiol* 2001; 22: 143-51.

37 Shutter L, Tong KA, Holshouser BA. Proton MRS in acute traumatic brain injury: role for glutamate/glutamine and choline for outcome prediction. *J Neurotrauma* 2004; 21: 1693-705.

38 Tollard E, Galanaud D, Perlbarg V, et al. Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: preliminary results. *Crit Care Med* 2009; 37: 1448-55.

39 Newcombe VF, Williams GB, Nortje J, et al. Analysis of acute traumatic axonal injury using diffusion tensor imaging. *Br J Neurosurg* 2007; 21: 340-8. ❑