Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report

FOREWORD

I am grateful that so many came together to help address this important topic. The United Kingdom Ministry of Defence was pleased to support this event as part of our duty of care to Service personnel, yet I recognise this subject is of national and international importance to our allies and across many fields of healthcare, employment and sporting activity.

It goes without saying that people, and specifically patients and their families, are the priority. The aim was a consensus that will help direct our further research and clinical innovation in mTBI prevention, detection and treatment pathways. The focus was to address diagnostic imaging modalities, but the discussion ranged much wider and deeper. It was important to me that all stakeholders had a voice. Moreover, it was critical that we could reach enough consensus on which to act, understanding where evidence is contested or at equipoise and that consensus may not mean unanimous acceptance.

I witnessed genuinely new knowledge being appreciated amongst the attendees, which was a success measure in itself, reflecting the value of bringing together national and international expertise. I also witnessed debate and challenge, those essential components for due diligence on the evidence presented. With the follow-up exchange of discussion and clarification, the summit has reached a series of consensus statements that provide a framework to align behind and drive forward the next steps.

I commend the consensus statements to you. I look forward to translating the summit outcomes into tangible actions that ultimately improve our patient outcomes, safety or experience.

Air Vice-Marshal Alastair N C Reid CB QHP
Surgeon General

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Setting a National Consensus for Managing Mild and Blast Traumatic Brain Injury: Post-Meeting Consensus Report

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* The opinions and assertions expressed herein are those of Dr David Brody and Dr Daniel Perl and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense.

SUMMARY OF RECOMMENDATIONS

1. **The military should consider the implementation of recruitment or pre-deployment screening as part of an independent research study**. Recruitment or pre-deployment screening of selected military personnel would allow for a comparison within the individual post-deployment and/or post-blast exposure or non-blast TBI event.
2. **The military should employ pre-emptive medical assessment for those experiencing an event likely to have caused m/bTBI.** This is rather than waiting for individuals to present later with symptoms.
3. **A diagnostic suite of tests incorporating imaging and neuroendocrine testing should be introduced within a 'one-stop research clinic' approach**. Expertise and resources would need to be carefully focussed. The one-stop research clinic should form part of a multi-modal clinical research protocol and the data collected should feed into a longitudinal research study.
4. **Regional Hubs are required** across the country with access to a one-stop research clinic. Hubs could be located in the South, the Midlands and Scotland based on research expertise and access to appropriate imaging facilities.
5. **Establish imaging and neuroendocrinology sub-groups for implementation**. Two sub-groups of experts will be established to help implement the recommendations from this Consensus Report, agree on protocols and/or technology to use, and ensure integration of research protocols within clinical settings. Joint coordination will facilitate collaboration and coherence.

INTRODUCTION

The purpose of the meeting held on Wednesday 15 January 2020 was to examine the current evidence for non-routine imaging and for neuroendocrine screening in the management of military personnel with brain injury and overlapping symptom domains. The Summit aimed to specifically address the relative utility of magnetoencephalography (MEG), diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) in the UK context.

Those in attendance at the meeting represented the following organisations/expertise:

- Defence Medical Services;
- Scientists from the United Kingdom, Unites States of America and Canada – many of whom work with the military;
- The UK National Health Service (NHS) – which would be responsible for implementing any new assessment protocols shown by research to have clinical utility in routine practice;
- The Chair of the Independent Medical Expert Group – the group which advises on medical aspects of the Armed Forces Compensation Scheme; and
- Clinicians who treat brain injury.

The approach during the day split the discussions into those about imaging and diagnosis first, followed by discussions about neuroendocrine testing. Both sessions started with a veteran's personal experience of mild traumatic brain injury to help inform the clinical context for discussions. These were then followed by presentations about the current science and clinical practice in the fields of clinical diagnosis, imaging, and neuroendocrine testing in the context of the current understanding of mTBI. The presentations led to discussions and debate which helped to establish the points of consensus outlined below, identified divergence of opinion and highlighted major uncertainties and gaps in knowledge.

Following the meeting, a brief Summary Report was produced and circulated to all attendees. Comments were then solicited for inclusion in this Consensus Report. The Consensus Report has been drafted with input from the attendees named as authors on this report.

POINTS OF CONSENSUS

Mild impact/acceleration TBI (mTBI) due to blunt head injury and blast-related TBI (bTBI) may not be pathologically identical. mTBI due to impact or acceleration is a well-recognised problem both in military and civilian populations, and many of the injury causations are similar between bTBI and mTBI. The majority of overall TBI are in the mild category. The military are more likely to be exposed to blast injury during conflict, and therefore this Consensus Report deals with bTBI as well as military-related mTBI (from non-blast events). Blast exposure appears to result in a different pathophysiological entity. Repeated mTBI or bTBI may also have cumulative effects that may be different to a single exposure to a blast or non-blast cause.

Overlap in symptoms between TBI and mental health conditions. The mental health conditions include Post-Traumatic Stress Disorder (PTSD), depression, anxiety and functional neurological disorders. TBI and mental health conditions (including PTSD) are leading causes of morbidity in service personnel and veterans. The disorders are complex, and the underlying pathophysiology is incompletely understood.

Currently there is no consensus or adoption of a diagnostic test that provides a 'signature' abnormality for m/bTBI. Severity of TBI from mild to moderate-severe can be defined using different categorisations that include factors such as acute level of consciousness (e.g. Glasgow Coma Scale), duration of post-traumatic amnesia (PTA) and acute neuroimaging findings (e.g. the Mayo classification). Currently there is no diagnostic test for m/bTBI that has been adopted. The MOD currently use a combination of the WHO and DoD definitions which are based solely on clinical criteria to diagnose mTBI in UK military personnel. Advanced imaging and formal neurocognitive testing are also used in some individuals, but not in a routine way.

Treat and diagnose the patient's symptoms rather than the suspected diagnosis or imaging results. At the current time, there is no biomarker to distinguish m/bTBI as distinct from PTSD. The two conditions often co-exist. Diagnosis is based on a history of one or more m/bTBI events, and treatment depends on the nature of the symptoms in individual patients, rather than imaging results. PTSD also remains a diagnosis made on purely clinical grounds. Baseline data (both imaging and neuroendocrinology) should be acquired in both these domains as part of future research (see Recommendations section).

Consideration of different cohorts for bTBI. There are three different military groups affected by blast-related TBI which require investigation:

1. Those currently presenting with symptoms compatible with a diagnosis of long-term sequelae of previous blast-related TBI and/or PTSD:
   - This cohort requires the development of an evidence-based management protocol/pathway which is agnostic of injury sequelae, and which acknowledges that both blast-related TBI and mental health conditions may be present.
   - This cohort could also be involved in the investigation of the longer term structural, functional and neuroendocrine changes which can be assessed against controls and other groups.
2. Those exposed to blast but with no long-term symptoms.
3. Population at risk of future blast-related TBI and who require enhanced mitigation strategies.
   - For this cohort it is important to better understand blast injury, particularly in terms of load, biomechanical effects, physiological responses and assessment of mitigation proposals.

Assessing the severity of the initial blast injury is difficult. A greater length of time since deployment may render it more difficult to recall the specific details related to blast exposure. Any future studies and clinical research protocols in this area should focus on serving military as well as veterans, with careful consideration of the severity of injury, and number and intensity of blast exposures.

Multi-modal imaging potentially offers new opportunities for the investigation and management of patients with military-related mTBI or bTBI.

1. Magnetic resonance imaging (MRI) is routinely used to assess the structural and functional impact of TBI.
   - Standard MRI approaches can identify many types of brain injury in both the acute and chronic phase. However, diffuse axonal injury and diffuse vascular injury are often missed unless more advanced MRI techniques are used.
   - Diffusion MRI has been widely applied to the study of diffuse axonal injury produced by civilian and military TBI. Diffusion tensor imaging (DTI) can identify subtle but important signatures of diffuse axonal injury, which can inform clinical management and outcome prediction.
   - Susceptibility weighted imaging (another type of MRI) is a sensitive way to identify diffuse vascular injury.
   - MRI scanners are available in almost all hospitals and protocols for advanced MRI acquisition are available on modern MRI scanners.
2. MEG appears to offer the potential to:
   - aid in diagnosis and in differentiating the pathophysiological consequences of m/bTBI from PTSD through 'signature' MEG abnormalities (noting however that TBI and PTSD often co-exist);
   - predict recovery outcomes and stratify patients e.g. those who will make a full recovery versus those who will continue to experience ongoing problems;
   - better understand the pathophysiology of these disorders; and
   - correlate with neuro-behavioural measures, e.g. symptom and neurophysiological scores.
3. MEG data acquisition and analysis techniques should be standardised, but MEG data acquisition is straightforward when acquiring resting-state data.
4. The importance of acting now and not waiting for the imaging technology to mature further was agreed.
5. MEG scans performed on those in the military affected by mTBI or bTBI should be undertaken as part of ethics committee-approved research studies and compared with advanced MRI.

There are deficiencies in the current imaging literature. Whilst the imaging field is progressing (both in terms of research and clinical use), there are discrepancies and deficiencies in the existing literature:

1. Many of the imaging studies are performed on varying versions of technologies without standardisation of data analysis methodologies. Technologies have evolved rapidly over recent years making some of the previously published data difficult to compare with recent studies.
2. Significant variability of protocol and scanner capabilities complicates sound meta-analysis being

reliably performed. Harmonisation methods are being developed by many groups globally, but there is currently no consensus as to the most appropriate methods of data analysis.
3. There is a lack of longitudinal data, particularly for MEG studies.
4. In some studies, images have been interpreted by non-specialists, putting the reliability of the conclusions into question.

There is potential to incorporate neuroendocrine testing in a multimodal clinical research pathway. Further discussion is required about how best to incorporate evidence-based neuroendocrine testing within the potential multimodal clinical research programme that will be taken forward.

POINTS FOR FURTHER DISCUSSION/ POINTS OF EQUIPOISE

The following points were established as requiring further discussions or investigation.

Study measures and study size. Imaging and neuroendocrine research studies in the literature have often included small patient groups, and rarely have been combined together in the same study. Global efforts to scan and test more individuals, with clearly defined clinical characteristics, with standardised protocols, and with pooling of data need to be pursued further.

Randomised Controlled Trials (RCTs) of treatments. Some believe that RCTs are required for the field to make progress, precisely because m/bTBI is a complex condition, hard to define, without a diagnostic investigative marker, with multiple co-morbidity, and without a clear pathology. It was noted that the only way to take management/treatment forward is well designed RCTs, preferably using just one treatment approach at the time so that one can be sure that any differences between the two samples are due to the intervention under study.

Longitudinal research is essential. Overall, the prognosis following m/bTBI is good. In a small minority, there can be a persistence and/or progression of symptoms, but there has not yet been an appropriate longitudinal study which follows the progression of abnormalities in the MEG signal, correlated with symptoms and cognitive deficits. The question remains as to whether a multi-modal longitudinal study should be used to assess the following:

1. MEG allied with the use of EEG – there is growing evidence of MEG's utility in the identification and differentiation of the pathophysiological changes found in mTBI and PTSD. Resting state MEG and MEG studies with cognitive loading are needed. Correlation with neuropsychological evaluation is essential (see below). The relative ubiquity of EEG across hospitals may prove advantageous if MEG derived abnormalities could be mirrored in EEG (albeit with perhaps lower sensitivity and vastly reduced spatial precision).
2. There are a number of areas that may prove particularly beneficial for the future assessment of m/bTBI using MRI:
   - The use of AI based software or computer aided diagnosis to assess advanced MRI (SWI and diffusion MRI, plus other novel sequences).
   - The use of high field strength magnets that can be used in clinical research protocols in multiple locations may be evaluated.
   - The use of diffusion MRI to assess white matter microstructure and identify evidence of diffuse axonal injury after m/bTBI.
   - The use of functional MRI to estimate the integrity of brain networks.
3. Assess the utility of neuropsychological testing in m/bTBI:
   - Research to identify the optimal cognitive loading testing required in the evaluation of individuals following m/bTBI.
   - Development and validation of neuropsychological/neurophysiological testing which may be more sensitive to subtle, but clinically meaningful changes in performance and functioning.
   - Assess the use of semi-structured interviews for assessment of mTBI and mental health across the studies to understand the broader neuropsychological symptom complex and relate to pathology.
4. Agree and assess a battery of neuroendocrine testing to measure the incidence and severity of dysfunction.
5. Accurate phenotyping of:
   - Military m/bTBI secondary to blast-related and non-blast-related mechanisms, that often co-occur.
   - Military moderate-severe TBI secondary to blast-related and non-blast-related mechanisms.
   - Military PTSD.
   - Military with both PTSD and m/bTBI (blast- and non-blast-related).
   - Military with blast injury but without symptoms of m/bTBI or PTSD.
   - Civilians with m/bTBI.
   - Civilians with PTSD.
   - Military and civilians with neither m/bTBI nor PTSD.

Test beyond the 'resting state'. Currently most published studies have reported resting state MEG data to assess abnormalities in those with mTBI, PTSD or both. While the recent literature has shifted focus from task-dependent to task-free paradigms, there is still a lot to be gained from the combined use of the two using study designs that are specific to the behavioural phenotype of the individual. Information may be gained, and more sensitive biomarkers found, via the use of cognitive tasks (working memory or attentional tasks) which probe patient symptoms.

Potential clinical research protocols for imaging and neuroendocrine testing. These are some suggestions for clinical research pathways which require further development and discussion:

1. Imaging and neuroendocrine testing undertaken before deployment so baseline data is established and then further testing employed post-deployment. Agreement needs to be reached on which individuals should receive recruitment or pre-deployment screening. Research may be required to provide criteria for selection, and there needs to be clear evidence from the research that markers are stable over time.
   - We need to further understand whether doing post-deployment imaging and neuroendocrine testing without baseline data is valuable. This may be more useful for imaging, as false positive results may often be seen in dynamic neuroendocrine tests depending on test and reference ranges used.
2. Serving military personnel with agreed diagnostic criteria for a particular clinical research protocol (e.g. imaging and neuroendocrine testing).
3. Veterans and civilians with similar entry criteria to an NHS clinical research pathway.

Selection of appropriate control groups. This needs to be considered in relation to the potential use of databases from around the world which contain MEG data from healthy control participants (e.g. Human Connectome Project, Omega, UK-MEG-partnership), which could provide a normative database against which to test for statistical differences in individuals with m/bTBI. This could also be considered in the context of randomised control trials where a comparator group is created by randomisation. Special care must be taken to recruit a military battlefield exposed, non-injured, comparator group.

RECOMMENDATIONS

The military should consider the implementation of recruitment or pre-deployment screening as part of an independent research study. Recruitment or pre-deployment screening of selected military personnel would allow for a comparison within the individual post-deployment and/or post-blast exposure (or non-blast TBI event). The following options should be considered:

1. Pre-recruitment history enquiring about previous m/bTBI.
2. Scanning:
   - Pre first deployment MEG and MRI screening of medium and high-risk servicemen and women. The risk stratification should be operationally based;
   - acutely following exposure to blast and non-blast injuries;
   - at an interval when there are persistent symptoms which could be attributed to m/bTBI; and
   - at retirement from active combat service and had exposure (or expected exposure) to blast or known to have had an m/bTBI.

A consideration of recruitment or pre-deployment scanning raises the likely prospect of picking up asymptomatic but potentially serious unknown neuroimaging abnormalities in the recruitment or pre-deployment scan. If such a study were to be undertaken in the UK, we would advise that scans are reviewed by an independent neuroradiologist and neurologist if abnormalities are identified. These independent reviewers would then decide if action should be taken.

Employ pre-emptive medical assessment for those experiencing an event likely to have caused m/bTBI. Based on experience from the United States, this may be preferable to waiting for individuals to present later with symptoms. It would also provide the opportunity to address immediate problems and reassure individuals about the likely good prognosis.

A diagnostic suite of tests incorporating imaging and neuroendocrine testing should be introduced within a 'one-stop research clinic' approach. Expertise and resources would need to be carefully focussed. The one-stop clinic should form part of a clinical research protocol and the data collected should feed into a multi-centre longitudinal research study.

1. Such a multi-modal prospective longitudinal study would help with determining the answers to the following questions:
   - Can m/bTBI and/or PTSD be differentiated from non-head injured controls by measuring brain activity?
   - Can m/bTBI and/or PTSD be pathophysiologically differentiated from non-head injured controls by novel imaging techniques?
   - Can biomarkers provide prognostic information for m/bTBI and/or PTSD?
   - To what extent do MEG, MRI and other imaging abnormalities correlate with symptoms and cognitive deficits?
   - Does analysis of MRI, MEG and EEG recordings allow network modelling to predict seizure risk after mTBI?
   - What is the prevalence of neuroendocrine dysfunction after mild or moderate-severe blast or non-blast TBI in military, what are the risk factors, and can it be predicted by clinical features or multi-modal imaging to enable targeted screening?
2. The following imaging would be conducted: structural imaging including conventional and advanced MRI techniques (including SWI and DTI), as well as functional imaging including the use of fMRI and MEG. Where available, high spatial resolution MRI using high and ultra-high field MRI and high gradient strength microstructure imaging could also be used.
3. The defined multimodal imaging as part of a one-stop clinic approach would standardise the pathway provided whilst minimising the number of interactions for patients.

Regional Hubs are required. To provide benefit across the country, regional hubs should be established for the one-stop research clinic where the suite of imaging and neuroendocrine testing can be carried out. Hubs could be located in the South, the

Midlands and Scotland (possibly London, Birmingham, Nottingham, and Glasgow), based on research expertise and access to appropriate imaging facilities.

Establish imaging and neuroendocrinology sub-groups for implementation. Two sub-groups of experts will be established to help implement the recommendations from this Consensus Report, agree on protocols and/or technology to use, and ensure integration of research pathways within clinical settings. It is important that the recommendations from the sub-groups are considered within the context of being able to deploy the research protocols within the NHS and, therefore, NHS participation is recommended. The sub-groups should clearly communicate with each other and coordinate activities for a seamless 'one-stop' experience.

CONCLUSION

There is an urgent clinical need to address the issues arising out of large numbers of military personnel and veterans with persistent symptoms of m/bTBI/PTSD. The exceptional promise of advanced imaging and new knowledge of neuroendocrine function in this area will only be translated into practice via an integrated, global, multi-modal research effort; acquiring new data, pooling existing data, integrating new experimental paradigms, initiating longitudinal metrics and standardising methods. The UK can achieve the first major step in achieving this translation to clinical practice through an appropriately resourced and supported research effort.

DECLARATION OF COMPETING INTERESTS

The following authors are employed by the Ministry of Defence: MC, IG, TGH, AM, ANCR, DS, AS, DRW.

AMJB is Director of the Centre for Blast Injury Studies that receives core funding from the Royal British Legion and support from the Ministry of Defence; AMJB serves on the project board of the Armed Services Trauma Rehabilitation Outcome Study funded by the Headley Court Trust, HM Treasury, Help for Heroes, Forces in Mind Trust, Blesma, the Limbless Veterans, and the Nuffield Trust for the Forces of the Crown.

APG has received research grant support from Pfizer.

AM is the Chair of the Clinical Reference Group for Complex Rehabilitation and Disability for NHS England.

JWS is Chair of the Independent Medical Expert Group, which makes recommendations concerning the Armed Forces Compensation Scheme.

DJS is a member of the Rugby Football Union Expert Concussion Panel.

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APPENDIX

Definitions and current status of imaging for TBI

Traumatic Brain Injury

- Traumatic brain injuries (TBIs) can be described as mild, moderate or severe and the mechanism of injury can be from blunt, penetrating or blast forces[1]. The severity, location, type, mechanism and physiological response to injury are also used as classifications of TBI[1].
- Clinical diagnosis of an acute injury is usually based on use of the Glasgow Coma Scale and sometimes the evaluation of neurobehavioural deficits[1,2,3].
- Imaging techniques can be used to help with diagnosis. Each of the below imaging techniques have been used in TBI patients, either individually or in combination. Some of these techniques are also utilised in research.

Computed Tomography Scanning

- Computed Tomography (CT) scanning is the modality of choice when assessing a head injury in the acute setting[3]. It is able to detect haemorrhage, intracranial injury, trauma-related fractures, swelling of the brain tissue and the presence of foreign bodies that are radio-opaque (e.g. shrapnel).
- Patients with mild TBI will have normal CT scans, so this modality is a poor discriminator for the presence or absence of mild TBI[2].

Magnetic Resonance Imaging

- Magnetic Resonance Imaging (MRI) is an imaging method that is non-invasive and allows the imaging of soft tissue and structures within the body[4]. Different tissues and structures have different

[1] Haydel, MJ (2018). BMJ Best Practice: Assessment of traumatic brain injury, acute. BMJ Publishing Group Ltd, London. https://bestpractice.bmj.com/topics/en-gb/515#referencePop1

[2] National Academies of Sciences, Engineering, and Medicine (2019). Evaluation of the Disability Determination Process for Traumatic Brain Injury in Veterans. The National Academies Press, Washington, DC. https://www.ncbi.nlm.nih.gov/books/NBK542602/pdf/Bookshelf_NBK542602.pdf

[3] National Institute for Health and Care Excellence (2019). NICE Clinical Guidelines No. 176: Head injury – assessment and early management. https://www.nice.org.uk/guidance/cg176

[4] Smith CJ, Rane R, Melendez L (2004). Operating Room. In Dyro JF (Ed.), *Clinical Engineering Handbook* (pages 376-384), Academic Press. https://www.sciencedirect.com/science/article/pii/B9780122265709500983

magnetic properties, allowing clinicians to tell them apart[5].

- MRI is considered superior to CT in terms of sensitivity for identifying haemorrhagic axonal injury and contusions. This includes in patients that have shown normal CT scans[2].
- MRI is more expensive than CT, and is usually less available in acute settings[2] with particular patient safety concerns in the acutely injured patient but provides optimal definition of brain structural anatomy.

Functional MRI

- Functional MRI (fMRI) can identify changes in communication between and within neural networks. It measures the differences in the MR signal between deoxygenated blood and oxygenated blood. When there is increased neural activity in a region, the signal from the local tissue changes as there is an increase in oxygenated blood to the region[6].
- Functional MRI provides information about brain function, which can be used following TBI. It has been primarily used to investigate dysfunction seen after TBI at the group level[7].

MRI: Diffusion Tensor Imaging

- Diffusion tensor imaging (DTI) is an advanced type of MRI that produces a measure of white matter structure in the brain[8]. DTI has been extensively used to investigate subtle but important effects of TBI and other types of brain injury. It has been shown to be useful in assessing post-traumatic damage to the structure of white matter connections in the brain.

Diffusion-Weighted Imaging

- Diffusion-Weighted Imaging (DWI) is able to map the complex architecture of fibres within the brain, at the submillimetric level.
- DWI is particularly used to help identify brain tissue that is ischaemic in the early stages of TBI[9].

Susceptibility Weighted Imaging

- Susceptibility-Weighted Imaging (SWI) is a technique which uses the differences in magnetic susceptibility of different compounds, for example iron, calcium and blood, to give contrast images[10,11].
- SWI aids the detection of diffuse axonal injury and microhaemorrhages. Small haemorrhages can be missed when using other MRI sequences[12].
- SWI MRI is a sensitive way to look at blood vessels and iron deposition within the brain[13]. This has been shown to be useful in the evaluation of Traumatic Brain Injury (TBI)[14].

Electroencephalography

- Electroencephalography (EEG) measures the synchronous activity of millions of neurons and allows assessment of electrical activity during different brain states (e.g. sleep, attentive wakefulness) where different frequency bands are often present[15].
- Pathological changes can also be identified, for example because of axonal injury during TBI[15].

Magnetoencephalography

- Magnetoencephalography (MEG) measures the magnetic field which is generated by neuronal electrical activity[16]. It provides high spatial and temporal resolution and is non-invasive[16,17].

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[5] National Institute of Biomedical Imaging and Bioengineering. Magnetic Resonance Imaging (MRI): https://www.nibib.nih.gov/science-education/science-topics/magnetic-resonance-imaging-mri [Accessed 30 April 2020]

[6] Bodanapally UK, Sours C, Zhuo J, Shanmuganathan K (2015). Imaging of Traumatic Brain Injury. *Radiologic Clinics of North America*, 53: 695-715. https://www.radiologic.theclinics.com/article/S0033-8389(15)00030-5/pdf

[7] Sharp DJ, Scott G, Leech R (2014). Network dysfunction after traumatic brain injury. *Nature Reviews. Neurology*, 10(3):156-66. https://www.nature.com/articles/nrneurol.2014.15

[8] Guye M, Chauvel P (2007). Developmental defects and pathophysiology. In Schapira AHV (Ed.), *Neurology and Clinical Neuroscience*. Mosby. https://www.sciencedirect.com/science/article/pii/B9780323033541500535

[9] Delouche A, Attye A, Heck O, Grand S, Kastler A, Lamalle L, Renard F, Krainik A. Diffusion MRI: Pitfalls, literature review and future directions of research in mild traumatic brain injury. *European Journal of Radiology*, 85: 25-30. https://www.ejradiology.com/article/S0720-048X(15)30146-7/fulltext

[10] Halefoglu AM, Yousem DM (2018). Susceptibility weighted imaging: Clinical applications and future directions. *World Journal of Radiology*, 10(4): 30-45. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5971274/

[11] Gonzalez RG (2017). MRI and MRA of ischemic stroke. In Caplan LR, Biller J, Leary MC, Lo EH, Thomas AJ, Yenari M, Zhang JH (Eds.), *Primer on Cerebrovascular Diseases*, Academic Press. https://www.sciencedirect.com/science/article/pii/B9780128030585001326

[12] Tate DF, Gusman M, Kini J, Reid M, Velez CS, Drennon AM, Cooper DB, Kennedy JE, Bowles AO, Bigler ED, Lewis JD, Ritter J, York GE (2017). Susceptibility weighted imaging and white matter abnormality findings in service members with persistent cognitive symptoms following mild traumatic brain injury. *Military Medicine*, 182: e1651. https://academic.oup.com/milmed/article/182/3-4/e1651/4099301

[13] Mittal S, Wu Z, Neelavalli J, Haacke EM (2009). Susceptibility-weighted imaging: technical aspects and clinical applications, part 2. *American Journal of Neuroradiology*, 30(2): 232-52. http://www.ajnr.org/content/30/2/232

[14] Tong KA, Ashwal S, Holshouser BA, Nickerson JP, Wall CJ, Shutter LA, Osterdock RJ, Haacke EM, Kido D (2004). Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. *Annals of Neurology*, 56(1): 36-50. https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.20123

[15] Rapp PE, Keyser DO, Albano A, Hernandez R, Gibson DB, Zambon RA, Hairston WD, Hughes JD, Krystal A, Nichols AS (2015). Traumatic brain injury detection using electrophysiological methods. *Frontiers in Human Neuroscience,* 9: 11. https://www.frontiersin.org/articles/10.3389/fnhum.2015.00011/full

[16] Singh SP (2014). Magnetoencephalography: Basic principles. *Annals of Indian Academy of Neurology*, 17(Suppl 1): S107-112. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4001219/

[17] Burgess RC (2019). Magnetoencephalography for localizing and characterizing the epileptic focus. In Levin KH, Chauvel P (Eds.), *Clinical Neurophysiology: Basis and technical aspects*. Elsevier. https://www.sciencedirect.com/science/article/pii/B9780444640321000138

Neuroendocrine testing in TBI

Neuroendocrinology is the field that looks at the nervous system's control of hormonal secretion and the control of the brain via hormones [18] . Neuroendocrine systems control many bodily functions.

Neuroendocrine dysfunction in TBI

- Many papers have considered neuroendocrine dysfunction after TBI, with the prevalence varying between studies. Potential differences are attributed to different sample populations, time since injury, injury severity, differences in the screening tests used, as well as confounding effects of other medications and other diseases[19,20].
- Hormonal screening can confirm significant pituitary hormone dysfunction, but usually needs repeat testing, with multiple dynamic endocrine tests needed for growth hormone and cortisol deficiency, and if a single test is used may in fact result in overdiagnosis[19,21].
- Pituitary dysfunction seen in the non-acute phase of TBI may recover in many patients within the first year after injury[19,22].
- Hypopituitarism in TBI patients may be the result of a number of potential mechanisms such as compression of the pituitary, vascular injury, increased intracranial pressure, direct trauma to the pituitary, and autoimmunity, genetic susceptibility and side effects of medications may play a role[19,20].
- Symptoms of pituitary hormone dysfunction after a TBI overlap with the neurological and psychiatric symptoms of the TBI itself[19].
- Even though pituitary hormone dysfunction may not be common after TBI, their diagnosis and treatment may have an important role in the individual's cognitive, psychological and functional recovery[22].
- Exposure to moderate-severe blast TBI appears to be a particular risk factor for development of pituitary dysfunction[21].

Testing and diagnosis

- TBI-induced hypopituitarism and other pituitary dysfunction is diagnosed in the same way as diagnosis of classical pituitary disease. There are variable patterns of hormone deficiencies/excess in patients with TBI-induced pituitary dysfunction and so each pituitary hormone needs to be tested for.
- Dynamic testing is required for some pituitary hormones - growth hormone, ACTH/cortisol and vasopressin/ADH[22].
- Evaluation of the functioning of the pituitary during the acute phase of injury, i.e. during the admission with TBI, is unnecessary because it is not clear at that stage whether the hormonal changes are because of an adaptive response or a deficiency[21]. Central adrenal insufficiency should only be investigated in the acute phase if it is suspected clinically[23].
- In the non-acute phase after injury, adrenal insufficiency is a priority for testing as although uncommon, it can be life-threatening[19,20,23,24].
- Testing of anterior and posterior pituitary dysfunction, are usually undertaken in the chronic phase of the injury as hypopituitarism can evolve over several months[20,24].

Measurements

- The availability of particular dynamic tests to diagnose growth hormone deficiency and central adrenal insufficiency may vary between countries and centres, and depend on resources available, while cut-off values vary between tests and may vary locally depending on the assays used[22]. Harmonisation of assays to national or international standards e.g. for growth hormone and cortisol helps this process.
- Defining cut-off values for diagnosis of growth hormone deficiency and central adrenal insufficiency is also made difficult because of the influences of other factors such as level of hypothalamic-pituitary damage, age, body mass index, and presence of other diseases such as diabetes mellitus.
- Several peripheral hormones (cortisol, testosterone, IGF-I) have circulating binding proteins whose levels can vary between individuals. While the binding proteins concentrations can be measured (cortisol binding globulin, SHBG,

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[18] Fink G, Pfaff DW, Levine JE (Eds). Handbook of Neuroendocrinology (2012). Academic Press. https://www.sciencedirect.com/book/9780123750976/handbook-of-neuroendocrinology#book-description

[19] Temizkan S, Kelestimur F (2019). A clinical and pathophysiological approach to traumatic brain injury-induced pituitary dysfunction. *Pituitary*, 22:220-228. https://link.springer.com/article/10.1007/s11102-019-00941-3

[20] Tritos NA, Yuen KCJ, Kelly DF, on behalf of the AACE Neuroendocrine and Pituitary Scientific Committee (2015). American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: A neuroendocrine approach to patients with traumatic brain injury. *Endocrine Practice*, 21(7):823-831. https://journals.aace.com/doi/10.4158/EP14567.DSCR

[21] Baxter D, Sharp DJ, Feeney C, Papadopoulou D, Ham TE, Jilka S, Hellyer PJ, Patel MC, Bennett AN, Mistlin A, McGilloway E, Midwinter M, Goldstone AP (2013). Pituitary dysfunction after blast traumatic brain injury: The UK BIOSAP study. *Annals of Neurology*. 74(4):527-36. https://onlinelibrary.wiley.com/doi/full/10.1002/ana.23958

[22] Tanriverdi F, Schneider HJ, Aimaretti G, Masel BE, Casanueva FF, Kelestimur F (2015). Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. *Endocrine Reviews*, 36(3): 305-342. https://academic.oup.com/edrv/article/36/3/305/2354717

[23] Tan CL, Alavi SA, Baldeweg SE, Belli A, Carson A, Feeney C, Goldstone AP, Greenwood R, Menon DK, Simpson HL, Toogood AA, Gurnell M, Hutchinson PJ (2017). The screening and management of pituitary dysfunction following traumatic brain injury in adults: British Neurotrauma Group guidance. *Journal of Neurology, Neurosurgery, and Psychiatry*. 88(11):971-981. https://jnnp.bmj.com/content/88/11/971.long

[24] Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A (2007). Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage. *JAMA*, 298(12): 1429-1438. https://jamanetwork.com/journals/jama/fullarticle/208915

IGFBP3), interpreting their influence on total hormone concentrations can be difficult, and tests for measuring free, biologically active hormones, are technically difficult, expensive and time-consuming[24].

- Basal pituitary hormone levels naturally vary because of circadian, pulsatile and situational changes in secretion of certain hormones e.g. from stress or food intake[22]. This requires rigorous attention to circumstances of sample collection and necessity to avoid making diagnoses based on single samples collected inappropriately.

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