Research on TBI and Chronic Traumatic Encephalopathy

Mårten Risling
Experimental Traumatology Unit
Department of Neuroscience Karolinska Institutet
Retzius väg 8, B1:5
SE-171 77 Stockholm
SWEDEN

Marten.Risling@ki.se

BASED ON CHAPTER 7 OF TR-HFM-193 "TRAUMATIC BRAIN INJURY IN A MILITARY OPERATIONAL SETTING", PUBLISHED JANUARY 2015, WHICH WAS PRODUCED TOGETHER WITH EMILIE CARRE, YUSHAN WANG AND THOMAS J. BALKIN, WITH INPUT FROM ALL OTHER TEAM MEMBERS.

ABSTRACT

This presentation is a review of research on TBI with special reference to military operational settings and the possibility to study TBI generated by weapons and detonations in animal models. The necessity and difficulties to translate between experimental data and real life clinical situations are discussed. Serological biomarkers and imaging techniques can be employed both for clinical diagnosis and to evaluate outcome in animal experiments and may therefore be important for translation between experimental and clinical data. There are several knowledge-gaps regarding long-term consequences after TBI. Repeated mild TBI has in some patients been shown to have a degenerative condition, Chronic Traumatic Encephalopathy, as a long-term consequence. Is this a concern in the military operational setting? Other important knowledge-gaps include differences between males and females, influence of age, influence of chronic inflammation and a more detailed understanding of mechanisms for secondary insults, such as edema formation.

1.0 INTRODUCTION

Trauma in a military operational setting may either be caused by weapons or by mechanisms that also apply in the civilian setting, such as road traffic accidents, sports activity, fall injuries etc. Trauma from firearms or from explosives can often be characterized by the high velocity. Energy delivery and absorption in the tissue takes place during a comparatively short time, even compared to road traffic accidents. The duration of the primary impact may be shorter than a millisecond. The impact may induce pressure waves, temporary cavity formation and shearing forces. Such mechanisms are difficult to study and understand in real life clinical settings. Physical disruption may not be pronounced in trauma that results in a mild TBI, but there are indications that white matter injury could occur in cases diagnosed as mild TBI. Animal experiments are useful for the understanding of complex injury mechanisms, but results from animal experimentation can be very difficult to translate to conditions in humans. The problems with translation with therefore be discussed during this lecture.

Long-term consequences of TBI are difficult to model with animal experiments. One of the most discussed long-term consequences of TBI is the Chronic Traumatic Encephalopathy (CTE) that has been observed in patients that have sustained a large number of impacts in sports such as American Football and Ice hockey. Is this a

relevant concern in military operational settings when servicemen are exposed to a number of blast waves or as a side effect to the use of heavy weapons, such as antitank rocket launchers?

2.0   BACKGROUND

The relationship between detonations and alterations in the function of the brain has been a concern since World War I. The large battles in Flanders generated enormous numbers of injuries and stress reactions. The distinction between neurological injuries and psychiatric disorders initiated by scenes at the battlefield created an intense debate at the time. It is still not fully clear whether the Shell-Shock syndrome should be regarded as a posttraumatic stress disorder (PTSD), a separate type of combat stress reaction or as a somatic reaction to blast waves, i.e. a blast induced traumatic brain injury (Jones, Fear et al. 2007). The use of improvised explosive devices (IED) in modern asymmetric warfare and terrorism has resulted in a growing number of soldiers and civilians that have either been directly exposed to blast waves or that suffer from the indirect effects of blast (Jaffee and Meyer 2009). The improved body and vehicle protection has evidently changed the scene significantly. Many of the individuals that are exposed to blasts today would probably have received lethal injuries had they not been protected by such armor. However, the modern protection may possibly also change the conditions for blast propagation in the body. For example, if the duration of a blast wave or the time to achieve peak blast pressure is changed, it may alter the injury pattern. Lessons can probably be learnt from the studies on BABT (behind armor blunt trauma) (Gryth, Rocksen et al. 2007, Roberts, Ward et al. 2007). The first experimental studies on biological effects of blast waves were published more than 60 years ago (Clemedson 1949). Fundamental information about the propagation of blast waves in the body, as well as their effects, is still absent today. However, recent studies have provided important knowledge about the distribution of inflammatory reactions after blasts in connection to body armor (Cernak 2010).

TBI is a very complex entity, often complicated by secondary injury cascades. Mild TBI is the dominating group of TBI. Most cases of mild TBI probably have very limited physical lesions, if any. However, many have functional effects that last for a considerable amount of time and the underlying factors remain to be established. The physics of the blast injury are very different compared to trauma the usual civilian setting. Blast induced brain injuries are often referred to as BINT (Blast Induced Neuro Trauma) and this term may then also include spinal injuries.

2.1   Blast Injury Mechanisms

Detonations represent a very complex event. An enormous amount of energy is released in a fraction of a second. Pressure waves can be amplified reflections from walls. The physical forces are usually unknown in real life events, but can be controlled in experiments. This represents one argument for the use of animal models for blast. Instruments such as the DARPA blast gauge mounted in helmets will most probably generate useful data that will enable a more detailed analysis of the physics in individual real life blast events. One way to understand the effects of a blast wave is to divide the mechanisms into:

- Effects of the primary blast wave. Thus the propagation of a supersonic pressure transient with short duration. The threshold for injuries is determined by factors such as peak pressure, duration and shape of the wave (reflections, underpressure, etc.). The effects in terms of bleeding in air filled organs such as the lungs and ears are well-known, but the potential effects on the central nervous system is still debated. For simple wave forms, i.e. the Friedländer type of wave, dose response curves (the Bowen curves) have been determined (Richmond, Damon et al. 1967, Richmond, Damon et al. 1967, Axelsson and Yelverton 1996, Cernak, Merkle et al. 2011).

- Secondary effects of blast, i.e. due to the impact of flying objects, such as shrapnel fragments, which can generate penetrating injuries. The proportion of such injuries was larger in previous conflicts, but seems to have been reduced by improvements in helmet construction. Outcome data from a large cohort of patients that survived penetrating brain injuries is available through the Vietnam Head injury study (Raymont, Salazar et al. 2011). This is probably the most detailed follow-up neurotrauma study that has ever been conducted and it could serve as model for how useful data should be collected.

- Tertiary effects of blast, i.e. the result of acceleration movements that may result in tissue shearing and diffuse injuries, such as diffuse axonal injuries (DAI).

- Quaternary effects of blast, the result of heat, smoke or emission of electromagnetic pulses.

2.2   Brief summary of Observations in Clinical Cases

The majority of the blast injury cases from the battlefield have sustained a trauma composed of more than one of these aforementioned blast injury mechanisms, e.g. primary blast combined with acceleration movements. However, exposure data are usually not available. Ongoing tests with acceleration sensor probes may change that situation. Severe blast related TBI with brain edema and vascular spasm (Armonda, Bell et al. 2006) could be assumed to be the result of a combination of more than one injury mechanism. The possible vascular propagation of blast waves into the brain and the possible effects on the functioning and perfusion of the blood-brain barrier has been suggested to be an important mechanism for blast (Chen and Huang 2011). It has been widely discussed whether the mild blast induced TBI should be regarded as a classic post-concussion syndrome or as a separate condition (Hoge, Goldberg et al. 2009, Lippa, Pastorek et al. 2010). The co-morbidity that is associated with PTSD and pain syndromes seems to be extensive. Also other psychiatric disorders appear to be overrepresented in veterans exposed to blast. Depression has recently been reported to be more common in female than male veterans suffering from effects of TBI (Iverson, Hendricks et al. 2011). Eardrum perforation and tinnitus has been reported in large numbers in veterans exposed to blast (Helfer, Jordan et al. 2011). Mild blast induced TBI has a higher proportion of hearing impairment compared to sports induced concussion (Belanger, Proctor-Weber et al. 2011). Also disturbance in vestibular function has been observed in veterans exposed to blast (Akin and Murnane 2011). The possibility that mild blast related TBI may also induce diffuse injuries such as DAI will most probably be evaluated in more detail through the use of modern imaging techniques, such as MRI with diffusion tensor imaging (DTI) protocols (Levin, Wilde et al. 2010). Available data so far is however not extensive enough to make any conclusions. Furthermore, the possibility that multiple mild TBI after blast exposures could induce long-term effects such as dementia should be considered (DeKosky, Ikonomovic et al. 2010) in carefully performed epidemiological studies.

3.0   EXPERIMENTAL DESIGN

3.1   Possible Strategies for Experimental Studies

Epidemiological data do not contain information of the relative importance of the different blast mechanisms. It is therefore important to generate data in carefully designed animal models. Such models can be selective reproductions of a primary blast, penetrating injuries from fragments, acceleration movements or combinations of such mechanisms. It is of crucial importance that the physical parameters of the employed models are well characterized so that the experiments can be reproduced in different laboratory settings. Ideally, pressure recordings should be calibrated by using the same equipment in several laboratories. The majority of the experimental studies have focused on effects of primary blast. A large number of different test situations have been employed. Tube systems with air overpressure chambers are common. Most shock and blast tubes used in current TBI animal models deal with the ideal primary blast wave, but lack the complexity of the real blast

generated by an IED on the battle field (Cernak and Noble-Haeusslein 2010). However, there appears to be a lack of consensus with regard to how the pressure in the various exposure systems should be measured and calibrated. Peak pressure and duration should be important components. However, to obtain pressure curves in different parts of the skull and body cavities with sensors that do not interfere with the propagation of the pressure waves is difficult (MediavillaVaras, Philippens et al. 2011). An experimental animal or a dummy is exposed to overpressure by a controlled perforation of a membrane that is a part of the air overpressure chamber. A few systems are specifically constructed to create complex waves and aim to mimic the specific signatures of different types of explosives or the situation in a protected vehicle (Cernak, Merkle et al. 2011). It is also possible to add body protection to the animals to evaluate systemic and regional effects of the blast (Cernak 2010). Other systems employ real explosives that usually add some quaternary blast components to the experiment. Some experimental setups provide a more rigorous control of acceleration movements to decrease tertiary blast effects. Conclusions from that type of studies indicate that DAI is a feature of acceleration movements rather than a typical effect from primary blast (Risling, Plantman et al. 2011). In most animal models of TBI, active astrogliosis, especially in the hippocampal regions of the brain, seem to be a common pathology. But whether it is caused by inflammation or it causes inflammation in the brain is not clear. Similar to a variety of neurodegenerative diseases, glutamate excitotoxicity has been implicated in various models TBI (Luo, Fei et al. 2011). Most recently, it has been shown that the cell surface expression of glutamate receptors, particularly the AMPA subtypes, were greatly changed after blast induced TBI in rat front cortex and hippocampus (Wang 2011). The cellular mechanisms that occur after ear injuries have been analyzed after blasts (Murai, Kirkegaard et al. 2008). However, the extent of cell death in the brain varies in different systems as well as under similar conditions in the same blast tube (Risling, Plantman et al. 2011). Therefore, the contribution of degeneration in mild blast TBI has yet to be settled. The impact of stress reactions on behavioural changes and modifications to injury markers after blasts has been evaluated in a rat model (Kamnaksh, Kovesdi et al. 2011). Thus, in summary, data from a number of animal studies seem to indicate that a systemic inflammatory response and delayed stress reactions may be an outcome from primary blasts. The number of experimental studies on blast TBI is rapidly growing and it is not possible to provide a full coverage in this context.

3.2 Examples of Models for Blast

A fairly large number of animal models have been used to replicate components of blast TBI (Risling and Davidsson 2012).

- Open field exposure. Examples here are the large-scale classical experiments in US in desert areas and ponds, employing large sets of animals of different species and sizes. These experiments determined thresholds for bleeding in air filled organs such as the lungs and intestines. The potential effects on the central nervous system were however not assessed. For simple wave forms, i.e. the Friedländer type of wave, dose response curves (the Bowen curves) were determined (White, Bowen et al. 1965) (Richmond, Damon et al. 1967, Richmond, Damon et al. 1967, Cernak, Merkle et al. 2011). The outdoor conditions limit control of the physiology of the experimental animals and may prevent proper tissue collection which is necessary for detailed studies on the brain. However, open field experiments may allow for realistic experiments with large animals and waveforms may be very relevant for simulation of IED. New models employing modified open field exposures include a Combat Zone-like blast scenery for mice (Rubovitch, Ten-Bosch et al. 2011) and a primate model (Lu, Ng et al. 2011).

- Blast tubes for explosives. During the 1950's large size blast tubes were created to study how construction details such as doors could withstand a blast wave that could correspond to the one from a nuclear detonation. However, the studies by Clemedson at the Swedish FOA (Swedish Defence Research Establishment) using a smaller blast tube (Clemedson and Criborn 1955) in which a charge of plastic explosive had biological effects from conventional explosions in focus. Clemedson and his

coworkers published a number of studies on vascular and respiratory effects of blast (Clemedson and Hultman 1954). After some time, this work was extended to include the central nervous system (Clemedson 1956) and the cerebral vasculature (Clemedson, Hartelius et al. 1957). The animals are mounted in metallic nets or fixed to a body protection in order to limit acceleration movements and there are no fragments. Therefore, secondary and tertiary blast effects should be very limited in this model. However, smoke and gas emission contributes with quaternary blast effects. One limitation is the short duration and very simple form of the blast wave. One way to modify the blast wave would be to extend the length of the tube and/or add reflective obstacles in the tube. One other modification would be to allow for predetermined acceleration. Recently the Walter Reed Army Institute of Research has published interesting studies on mild BINT in swine exposed in a large size blast tube (de Lanerolle, Bandak et al. 2011).

- Shock tubes with compressed air or gas. Systems with compressed air were used already in the 1950´s (Celander, Clemedson et al. 1955). Most systems comprise 2 chambers, separated by a membrane. Compressed gas is loaded into one of these chambers, referred to the overpressure chamber or the driver section, which is separated from the other chamber, referred to as the main section or the driven section, by a diaphragm. The object, i.e. the experimental animal, is positioned somewhere in the main section. The operator can rupture the diaphragm and the compressed gas enters the main section and simulates a propagating blast wave. The main section is usually several meters long. If several overpressure chambers are positioned in a series rather complex waveforms can be created. The duration of the pulse is usually longer and the peak pressure is much lower than in the Clemedson tube. One advantage associated with this type of shock tube is the absence of quaternary blast effects as well as other disadvantages of explosives. However, this advantage can also be regarded as a disadvantage. There are a number of modifications of the shock tube design and there seems to be a need to calibrate the different systems. Well-documented modern shock tubes can for instance be found at the Walter Reed institute (Long, Bentley et al. 2009) and the US Naval Medical Research Center (Chavko, Koller et al. 2007, Chavko, Watanabe et al. 2011). One very sophisticated shock tube system has been installed at the Applied Physics Laboratory at Johns Hopkins University (Cernak, Merkle et al. 2011).

- Models for penetrating TBI, with possible relevance for secondary blast. The penetrating ballistic brain injury model both the permanent injury tract created by the path of the bullet itself and the large temporary cavity generated by energy dissipation from a penetrating missile. The model has been characterized in a large number of studies and can presumably generate important knowledge about cavity formation during fragment penetration, although the model was specifically constructed to simulate effects of NATO 7.62 mm rounds (Williams, Hartings et al. 2005, Williams, Wei et al. 2007) and is not aimed for studies on mildTBI. One other device for studies on penetration of the skull and brain tissue by shrapnel fragments is the model for controlled penetrating TBI at a speed of 100 m/s. A lead bullet is accelerated by air pressure in a specially designed rifle and impacts a secondary projectile (Plantman, Ng et al. 2012). The base of the projectile is surrounded by compressible ring that provides control of the penetration depth into the brain. However, this is not a model intended for mild blast TBI.

- Models for acceleration/deceleration TBI, with possible relevance for tertiary blast: The rotational weight drop model that was developed by Marmarou and coworkers (Foda and Marmarou 1994, Marmarou, Foda et al. 1994) has generated very important data on development of diffuse brain injuries, including an improved understanding of diffuse axonal injury (DAI) (Povlishock, Marmarou et al. 1997). However, this model combines DAI with a contusion injury, which makes the model less useful for selective studies on DAI. A number of acceleration devices have been developed for work in rodents, but the majority seems to result in more severe injuries with meningeal bleedings (Hamberger, Viano et al. 2009). A model aimed for threshold studies has been described by Davidsson (Davidsson and Risling 2011). The signature injury with this model is diffuse axonal injuries in the corpus callosum,

subcortical white matter and the brain stem. The absence of cell death and excessive bleedings indicate that this is a mild TBI and effects on behaviour are indeed limited. Thus, this model can add knowledge about mechanisms and thresholds for acceleration induced mild TBI and such data can be relevant for the understanding of consequences of tertiary blast.

3.3   Systemic Reactions, Including Stress and Inflammation

The studies of Cernak have shown that blast-induced neurotrauma (BINT) can be a systemic reaction to blast (Cernak 2010). General inflammatory reactions from the primary blast can contribute to the reactions of the brain. The propagation of pressure waves through the body in blast trauma is still a subject of controversy. Important data can be retrieved by carefully designed experiments employing partial body protection (Cernak, 2010).

Refined behavioural tests with a high sensitivity for stress reactions similar to posttraumatic stress will be important in the future work with BINT (Kovesdi, Gyorgy et al. 2011, Kwon, Kovesdi et al. 2011). Experimental exposure to primary blast has been shown to induce changes in brain stem nuclei similar to changes that can be expected in stress and depression. These changes include both the monoaminergic system (Kawa, Arborelius et al. 2015) and the peptide galanin with receptors (Kawa, Barde et al. 2016). Such data indicate molecular similarities between the response to blast TBI and posttraumatic stress. A number of additional studies are obviously necessary to analyse the potential biochemical links between TBI and stress responses.

4.0   TRANSLATION

4.1   Translation Between Clinical and Experimental Data

The most central problem, however, is that exposure data from actual clinical situations are lacking. Acceleration probes mounted in helmets (Rigby, Wong et al. 2011) may help to solve this problem and if the same type of sensors will be implanted for use in animal experiments translation of data may be facilitated. One other way to accomplish a better translation between animal experiments and the clinic would be to employ the same methodology for analysis (Agoston, Risling et al. 2012). Imaging with MRI and systematic use of biomarkers can be used in both settings and help to bridge the gap between the lab bench and the hospital bed. Computer simulation represent a possible link between experiments and studies of human cases. However, in order for mathematical simulations to be completely useful, the predictions will most likely have to be validated by detailed data from animal experiments. Some aspects of neurotrauma can conceivably be studied in vitro. However, factors such as systemic response, brain oedema, inflammation, vasospasm or changes in synaptic transmission and behaviour must be evaluated in experimental animals. The lack of exposure data from clinical cases makes it very difficult to propose suitable models for experimental studies. Experimental studies are necessary to generate a full understanding of thresholds and consequences, as well as injury profiles for primary/secondary/tertiary/quaternary blast injuries. One problem that results when comparing clinical and experimental studies is the mismatch between the employed techniques. It would be of value if experimental studies could employ similar imaging protocols to those used in the clinical setting. Biomarkers may also be very useful to connect clinical and experimental studies (Gyorgy, Ling et al. 2011). Injury reconstruction (Kleiven 2007) and finite element modelling can also be of value to bridge the gap between clinical data and studies on experimental animals, provided that they can be validated by biological findings. With carefully designed models and thoroughly evaluated animal data it should be possible to achieve a translation of data between animal and clinical data. Sometimes an animal model can be used to make more detailed mapping of a molecule that has been implicated in a clinical to be of interest for the outcome of TBI. For example, single nucleotide polymorphisms for the BDNF (brain derived neurotrophic factor) gene was shown to have an impact for the

long-term outcome after penetrating TBI in Vietnam Veterans (Rostami, Krueger et al. 2011) and a rodent model was subsequently used to map the distribution of this growth factor and its receptors (Rostami, Krueger et al. 2014).

4.2   Translation Between Different Experiments

The lack of reproducibility in research using animal models represents an area of concern and can be attributed to a large number of factors (Knight 2008, ter Riet, Korevaar et al. 2012). Small variations in the employed protocols can generate different results of the experiment. It is therefore important to repeat crucial experiments and check that the results actually can be reproduced. The choice of the animal species or strain can obviously have a significant impact on the outcome of the experimental injury. Differences in body size and the geometry of the skull can be assumed to represent critical factors in experimental design. For example, experiments with rotational acceleration are very dependent on the distance to the axis of rotation, thus a larger brain may be far less resistant to rotational injury. Different rat strains may exhibit different inflammatory responses and reactions to TBI (Bellander, Lidman et al. 2010). Thus, the selection of strain can have a significant impact on the result. Transgenic mice and knockout models can be used to identify the impact of individual genes. To employ a number of common data elements can facilitate the translation between experiments at different laboratories (Smith, Hicks et al. 2015).

5.0   CHRONIC TRAUMATIC ENCEPHALOPATHY AND REPEATED INJURY

TBI is well known consequence in boxing and other contact sports (Ling, Hardy et al. 2015), such as American football and Ice Hockey. Short term sequelae can be acute severe TBI with hematoma that may lead to death. Mild TBI is obviously much a more common outcome in sports medicine that can cause functional disturbance and possibly axonal injury. The importance of recurrent mild TBI for development of late injuries has been documented in sports medicine (Guskiewicz, Marshall et al. 2005). The punch drunk syndrome was described many years ago. The term chronic traumatic encephalopathy (CTE) has been used in recent years to define a specific degenerative disorder in the brain, characterized by deposits of tau protein (Stein, Alvarez et al. 2014). CTE has been associated with a variety of types of repetitive head trauma, most frequently contact sports. In cases published to date, the mean length of exposure to repetitive head trauma was around 15 years (Stein, Alvarez et al. 2015). The long latency between injury and onset of clinical symptoms makes it difficult to model CTE in rodents.

Most available evidence seem to indicate that impacts are necessary to induce the injuries that might lead to CTE and that side-pressures from weapons or repeated blast exposures are less likely to induce CTE. Repeated blast has been evaluated with regard to non-auditory, pulmonary, and fatality. It has been reported that a decrease in injury tolerance with each subsequent blast exposure (Panzer, Bass et al. 2012). Säljö and co-workers reported that the side-pressure from heavy weapons could induce neuropathological changes in experimental animals (Saljo, Mayorga et al. 2011). However, such effects could not be verified in army officers were exposed to repeated firing of a FH77B howitzer or a bazooka (Blennow, Jonsson et al. 2011). The relationship between repeated exposure to blast overpressure and neurological function has been examined in the context of breacher training (Carr, Polejaeva et al. 2015, Carr, Stone et al. 2016). The instructors are in focus since they are exposed to the largest number of events. The data from breacher training are not conclusive, so far, but such studies should be of significant interest for the understanding of the possible effects of repeated mild blast events.

6.0   CONCLUDING REMARKS

There are several remaining knowledge-gaps in research on TBI, such as the long-term consequences of different types of TBI. Differences between males and females, as well as age aspects are other important areas of research. The mechanisms for secondary insults such as oedema are still very relevant, since such conditions might be targeted with new treatments.

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