Chapter XI. Other Forms of Injury:

Section D: Overpressure Concussion

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Much research has been carried out defining the molecular mechanisms, pathophysiology, and histopathology of traumatic brain injury.

The history of medical management of concussion involves significant contributions by physicians and surgeons involved in Military Medicine including those injuries sustained to the skull both and without helmet protection (1-2). Sport injuries to the central nervous system have been most dramatically defined in those concussion injuries to professional prize fighters and led to analysis of the contributions of chronic repetitive injuries to the brain compared to single dramatic explosive injury (3). The description of the contra-coup injury was dramatically described in Neurosurgery and Neuropathology literature in the early decades of the 20th Century (1). Traumatic injury to one side of the skull resulted in measurable damage to the opposite side of the skull and was defined as that associated with movement of the brain inside the skull against the contralateral inside of the calvaria (1). Trauma to the brain itself, and also from bleeding associated with stretching the vasculature during concussive injuries led to description of injury related subdural hematomas and intracerebral bleeding (4).

There has been a separate literature dealing with the "shaken-baby" syndrome resulting from cranial injuries from child abuse (2-3). The infant brain is protected by bones in the skull, but the sutures are incomplete during the first year after birth. This results in some increased plasticity of the brain inside the skull, but also to decrease protective capacity of the incompletely ossified cranial plates. Cranial injury in children from automobile accidents including neck injuries, as the head can be thrown forward even when the body is restrained in a car seat, result in both cervical spine and brain injury.

The consequences of traumatic brain injury are both acute and chronic. Analysis of acute injuries is now routinely carried out with examination of athlete suffering football, ice-hockey, or other head traumas, and has led to the induction of a "Concussion Protocol" (3). Basic cognitive function analysis is carried out similar to that as part of a routine comprehensive physical exam. Cognitive awareness including ability to rapidly identify time, place, and person is initiated, and then analysis of acute and chronic memory function combined with other aspects of the comprehensive neurological exam including testing of function of all cranial nerves, and then central axis and peripheral muscular and sensory function. Cerebellar ataxia is measured for lower extremities by walking, and for upper extremities by testing rapid coordinated structured movements such as touching the examiner's finger, and then rapidly touching one's nose, repeating this multiple times (3).

Because of the internal nature of concussion, cranial damage may not be fully apparent from outside injury (bruises, hematomas, blood clots that are visible) (5). Prevention of head trauma from concussion has been decreased in bicycle riders by the importance of protective helmets, and in student, as well as, professional athletes by using head protection (6). Trauma to the neck cannot be prevented by helmets, and neck trauma is a severe complication of concussive head injury in athletes, as well as, military personnel.

Irradiation effects on the central nervous system compound and exacerbate concussive injury.

The acute and chronic effects of irradiation of the brain and spinal cord are described in detail in other chapters in this web-based textbook. Interaction of concussion-based trauma with whole brain irradiation has gained importance in recent years from experience with nuclear reactor accidents, and concern for possible radiation terrorism. Molecular and cellular events occurring in the brain parenchyma, as well as, vasculature have been described including the induction of stress response genes, inflammatory cytokines, and is involved in cellular death pathways including: apoptosis, necroptosis, and ferroptosis (7). A significant overlap of activation of these pathways with those activated by ionizing irradiation are consistent with observations that radiation exposure below doses associated with clinical symptomatology, can result in clinical symptoms in a setting of combined concussion injury.

Animal models for studying combined traumatic brain injury and irradiation have been described. The "controlled-cortical impact" model has been applied to studies of traumatic brain injury induced apoptosis and the effect of anti-apoptotic drugs (GS-nitroxides including XJB-5-131) on ameliorating both the pathophysiologic and behavioral consequences of traumatic brain injury (8). Methods for these experimental models are well described in this publication. Radiation effect on the brain can also be studied using the methodology described in this manuscript.

There is also a significant body of literature describing radiation effects on the brain (9-10) in both rat and mouse model systems, irradiation-induced antioxidants has been described including: Manganese Superoxide Dismutase, and synthesis of glutathione (9). Superoxide Dismutase deficient mice have been shown to be more susceptible to brain irradiation. Specific areas of the brain including the hippocampus are particularly sensitive to ionizing irradiation. Clinical correlates studied in these animal models have led to implementation of whole brain irradiation protocols shielding the hippocampus (11). These data are described in detail in the chapter of this web-based textbook dealing with brain irradiation.

Methodologies for studying the effects of combined injury: concussion and ionizing irradiation.

The methods of experimental protocols dealing with the interaction of concussive injuries with irradiation would follow rules similar to those studying the interaction of two drugs with each other. The concept of synergy is in which subliminal doses of one drug combined with measurable doses of a second drug result in a greater effect than either of the two alone can be carried out with quantitative delivery of ionizing irradiation compared to concussive brain injury (using the controlled cortical impact model). The ability to deliver a specific concussive force to rodents in which the calvarial is removed, and the exposed brain subjected to specific concussive force leads to experiments in which quantitation of the outcomes from each concussive force group can be studied alone, or in combination with brain irradiation delivered either before or after the concussion leads to a useful model system (8).

A useful assay for the combined effects of concussion and radiation should include: pathologic, histopathologic, pathophysiologic, and also cognitive behavior studies. In rodent models, brain tissue can be removed and assayed for structural abnormalities, apoptosis in brain parenchyma compared to endothelial cells (apotag assay), as well as, gross and microscopic evidence of cell

destruction. Brain swelling can be measured in volume displacement assays and in tissue weight measurement. Neurophysiologic measurements of brain function have recently been applied to study of brain irradiation (8).

The assays for neurotransmission measurement require microneedle puncture specific neurons, measurement of action potential, and quantitation of individual neuron function within specific areas of the brain (12).

The experimental paradigm for study of combined injury should follow basic rules testing the effect of two independent agents.

As a first set of experiments, whole brain irradiation compared to total body irradiation can be delivered to mice (or rats) of a specific mouse strain in which baseline information is already published and available. For example, C57BL/6J mice have been intensively studied by radiation biologists with expertise in analysis of brain function (9-10). A dose response curve can be carried out with measurement of several different parameters including those associated with cell death, cell swelling, gross and microscopic histopathologic changes, and the cognitive behavior studies in recovering animals (Morris Water Maze, Novel Object Recognition, Fear Conditioning, and others) (8).

Large numbers of animals may be required to create a dose response curve. Careful attention to uniformity of animals by gender, age, and weight should be part of these experiments.

Once dose response curves for isolated brain irradiation compared to total body irradiation are established, this baseline data can be used for comparison with concussion injury.

A similar set of experiments should be carried out then with controlled cortical impact measurements in the same mouse strain using the same gender, age, and weight animals. A dose response curve can be generated in the same way, as it was done above with irradiation.

Once these two data sets are established, it is recommended that a dose of irradiation (whether whole brain or total body) on the linear portion of the dose response curve should be selected for experiments with combined injury. One can then use this established irradiation dose, and try to keep this dose constant, while then subjecting experimental animals to a dose response curve of controlled cortical impact, as a measurement of brain trauma. A major question in these studies is whether the controlled cortical impact should be carried out before or after irradiation. The surgical trauma of exposing the brain (removal of calvarium) represents an addition of yet another (third) component of a 3-part combined injury (wound) in addition to concussion and irradiation; therefore, for such experiments investigators may wish to use a model in which the calvarium is not removed. Animals, then, would be subjected to controlled cortical impact either before or after brain or total body irradiation. It should be noted that the method for immobilizing animals for controlled cortical impact studies, as well as, for isolated brain or total body irradiation is also a source of stress. For this reason, investigators have paid attention to the issue of whether or not to use general anesthesia, and how long animals should be immobilized for, either the cortical impact, the radiation, or both modalities.

Recent studies have shown that the dose rate from a Cesium-source animal irradiator (Gamma-Cel, Mark IV) can be increased by removing the filter. However, this changes the spectrum of orthovoltage energies (13-14). However, increasing the dose rate vastly decreases the time for immobilization and restriction of mice in the irradiator and has been shown to mediate the stress of immobilization of animals for prolonged periods to deliver a total body irradiation dose of 9.25 Gy. The increase in dose rates from the standard 7.5 cGy/minute to 360 cGy/per minute reduced the time in the irradiator from 13 to 3 minutes, and this change in protocol was associated with a greater reproducibility of the total body irradiation dose response curve in adult C57BL/6J mice (14). The effects of dose rate on the combined injury of concussion plus irradiation may be another variable for consideration (15) .

A recent publication indicated that dose rate changes varying from 0.15 cGy per minute up to 15 cGy per minute (mimicking solar proton irradiation of space flight) (16) was not associated with detectable effects. While these studies were not carried out in the setting of combined injury, all investigators should be acutely aware of the potential effect of changing dose rate on the biological outcomes of combined injury experiments.

Practical considerations in dealing with patients, who have had both concussive brain injury and ionizing irradiation exposure.

Triage procedures for victims of radiation terrorist events will require Emergency Room physicians to consider all forms of combined injury. Combined injury may include multiple forms of trauma in addition to irradiation, and these are discussed in other chapters within this web-based textbook. However, in those individuals, who have suffered concussive brain injury and ionizing irradiation, the general principles for emergency room triage will be followed. When available, history and analysis of behavior changes, as well as, neurological functional changes since radiation exposure will be part of the triage procedure. Those, patients felt to be at risk for concussive brain injury in addition to irradiation will be triaged along with other patients, who have an estimated radiation exposure dose that may exceed or be less than that associated with that degree of traumatic brain injury.

Administration of radiation mitigators follows procedures for estimation of safety in the studying of combined injury compared to the situation of irradiation alone. Because of the complicated nature of radiation terrorist event by induced injuries, all of these events must be considered.

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