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THE NATURE OF RADIATION INDUCED BRAIN SWELLING

by

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Traditional studies of radiation injury have emphasized cytokinetic injury to cell replication. However, most investigators recognize that other damage may limit the amount of radiation which may be safely delivered to a given organ. Examples of non-cytokinetic radiation injury can be seen in radiation hepatitis, where central vein thrombosis limits the safe radiation to the liver. Brain radiation dose is also limited by other than primary cytokinetic consideration. It is well recognized that cerebral injury limits radiation therapy for primary or metastatic brain tumors. Is this injury related to brain swelling? If the brain injury mechanism could be more clearly defined, it may be possible to design rational therapeutic techniques to protect normal brain during radiotherapy and, thereby, increase the safe radiation dose which can be delivered to a brain tumor. With these points in mind, based on our previous experience in distinguishing water from tin induced edema in the experimental animal, we set out to define the brain red cell and albumin spaces in relationship to radiotherapy in the experimental animal.

METHODS

100 gram female white rats (NLR strain) were anesthetized (pentobarbital) and given radiotherapy from a 220 kev 15 MA machine (406 rads per minute using a 0.5mm cu and 1mm Al filters) in one single dose which was collimated to include only the head of the animal. Six animals in each group were given 100, 500, 1,000, 5,000, 10,000, 15,000, 20,000 and 40,000 rads in a single dose delivered only to the head. The 40,000 rad animals all expired in less than 24 hours. The remaining groups at 24 hours received Fe-59 tagged donor red cells and I-131 labeled human serum albumin as in our previous experiments on water and tin induced brain swelling in the experimental animal.¹ Five minutes following the tail vein injection of the radiotracer the animals

were sacrificed by immersion in liquid nitrogen, the brains removed. One hemisphere was assayed for radioactivity and the other was processed for histological studies. Control animals for each group were treated identically including anesthesia and positioning under the radiotherapy device but receiving no radiation. Spaces are calculated by the standard techniques as previously described.

RESULTS

With 100-500 rads we were able to demonstrate a decrease in the red cell mass per unit brain similar to that seen in water induced brain edema.¹ This was associated by a slight decrease in the albumin spaces suggesting an absolute decrease in the intravascular volume. Increasing the dose to 1,000 rads caused a marked decrease in brain red cell mass (consistent with rather severe brain edema and compression of the vascular space by the swollen brain), associated with increase in the albumin space consistent with increased vascular permeability to protein. Increasing the dose range above 10,000, i.e. the 15,000 and 20,000 rad animals demonstrated a remarkable increase in the brain red cell mass per unit brain (Figure 1) related to intracerebral edema and microhemorrhage. These observations are confirmed by histologic sections (Figure 2).

DISCUSSION

Previous investigators² demonstrated an increase in 5 minute albumin space in rats receiving 10,000 rad. However, this was not associated with what they considered to be a breakdown of the blood brain barrier as evidenced by the standard trypan blue accretion by the brain substance. With 100 rad we have demonstrated a dose dependent decrease in brain red cell mass and albumin space similar to that seen in water intoxication. With larger doses (1,000 - 10,000 rad) there is a progressive increase in the albumin space with a persistent decrease in red cell mass suggesting

that the nature of the cerebral dysfunction is related to endothelial damage akin to tin induced edema which causes a similar redistribution in brain albumin and red cell spaces due to primary endothelial damage. Larger radiation doses (10,000 rad) caused a frank increase in both the albumin and red cell spaces. Histologic correlation confirms that red cell diaphoresis at this dose level.

These findings suggest that changes in the cerebral compartments occur at a relatively low radiation dose in comparison with what has previously been considered. At doses of 100 rad, brain swelling occurs without a breakdown in the endothelial barrier to albumin. Larger doses are characterized by an increased albumin and decreased red cell space characteristic of endothelial damage with plasma protein leak.

Radiation in other tissues usually causes an increase in the red cell space. The fact that this does not occur in brain is not surprising when one appreciates the characteristic of brain edema is a decreased vascular volume. Thus, radiation induced brain swelling is due to frank brain edema rather than vascular distention. The recognition that brain swelling may occur with relatively low dose radiotherapy in the experimental animal suggests that attempts at radioprotection may be a reasonable adjunct to cerebral radiotherapy. Specifically, the recognition that the nature of the defect varies with the radiation dose suggests that at low radiation doses brain swelling is associated with osmotic transport resembling water intoxication, while larger doses are characterized by a frank leak of plasma protein into the extravascular space, and still larger dose are associated with frank microhemorrhage. These studies suggest that these tracer techniques may be used to identify more subtle derangement of brain spaces than

are now diagnosed at the clinical level. Once identified the cerebral radioprotective effect of dose fractionation and specific drugs (e.g. osmotic diuresis, steroids, or lowering blood CO_2 through hyperventilation) may be profitably investigated.

Figure 1

ABSTRACT

Brain red cell and albumin space were used to define the nature of brain swelling following brain radiation in the 100 gram white rat. This relatively sensitive indicator of brain edema revealed a decrease in brain vascular volume at 100-500 rad similar to the defect seen in water intoxication. At 1,000-10,000 rad the decreased red cell mass was associated with a progressive (dose dependent) increase in the brain albumin space similar to the endothelial defect seen in the tin induced brain edema. Massive radiation (15,000 - 20,000 rad) resulted in an increase in both the albumin and red cell spaces, associated with frank red cell diaphoresis. Thus, brain swelling occurs at rather low radiation dose in the normal rat and the nature of the defect changes with increasing radiation dose. These observations are pre-requisite to correlative clinical studies evaluating therapeutic attempts to protect normal brain during cerebral radiotherapy.

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