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Effects of Cobalt Radiation on the Rat Brain

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Abstract: This invesrigation was carried out to follow up radiation induced changes in brain of Wistar rats. Rats (weighing 160 to 180 g) were randomly divided into 4 groups of 6 each. Three groups were irradiated with 5 y, 7.5 and 12 Gy. The fourth group served as normal control. Results demonstrated dosage dependent changes in different parts of the brain tissue. Histopathological studies of the central nervous system revealed radiation-induced lesions early after exposure with congestion and edema. Marked and irreversible changes included gliosis, necrosis of neurons and vacuoles which were more pronounced in the subcortical regions. It was concluded that radiation injury is associated with irreversible damage to the neural stem cell compartment and induced apoptosis and depletion of oligodendrocytes may cause vacuolation and demyelination in brain.

Key words: Irradiation · Rat · Necrosis · Gliosis · Brain tissue

INTRODUCTION

Combination of surgery, chemo therap y and radiation treatment are the mainstay of the modern cancer therapy [1,2]. Studies from exposed human and animals indicate that radiation from cobalt can affect a wide variety of tissues particularly those with greater levels of cellular turnover and divisions [3-5]. Tissue tolerance of the normal brain is very limited and radiation doses have to be tailored to minimize the deleterious effect on the nervous system. Radiation necrosis and cerebral atrophy are considered long term complications of radio-therapy that occur from month to decades after radiation treatment [6-8]. Diffuse cerebral atrophy clinically is associated with cognitive impairment, personality changes and gait disturbance. Currently, there is no effective treatment for radiation-induced cognitive decline [2,9]. Necrosis and inflammation were the key features of high dose radiation injury. Radiation necrosis is coagulative and predominantly affect white matter. The coagulative necrosis is due to small artery injury and thrombotic occlusion. It has been hypothesized that irradiation of the brain has an additional risk factor for the development direct injury toglial cells. Exposure to the moderately low doses of cobalt 60 radiation has resulted in decreased body weight [10 - 12]. The purpose of the present study was to investigate the impact of cobalt irradiation on the brain; the most eloquent tissue of the body and to enhance understanding of the brain cellular response to cobalt irradiation.

MATERIALS AND METHODS

Twenty four adult male and female Wistar rats were used in this experiment. Animals were housed under standardized conditions for light and temperature. A commercially prepared diet and clean drinking water were provided *ad libitum*. Rats were anesthesized with an intraperitoneal injection of mixture of ketamin (80mg/kg) and xylazine (8 mg/kg) prior to irradiation. Rats were randomly divided into four groups (n=6/group) and three groups were irradiated with 5, 7.5 and 12 Gy, on the whole body for 10 to 15 minutes. The fourth group served as normal control. Irradiation was performed through the use of cobalt60 rays with a device from a Canadian company Tretron, model Phoenix,belonging to the Cancer Treatment Center of Omid hospital, in Urmia. The cobalt radiation was administered to the body using a 250 kv orthovoltage system. A custom designed positioning device based on the standard steriolactic frame was used so that six animals could be simultaneously irradiated. Dosimetry was performed by implanting lithium fluoride

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thermoluminescent dosimeters into various areas. The corrected dose rate was determined to be 205/69c GY/min and irradiated with a distance of 7.5 cm on the field of 35x35 in the dorsoventrl axis.

During 30 days after irradiation behavioural changes and other changes, mainly on the body surface and lethality were recorded. The surviving rats at the end of experiment were sacrificed with carbon dioxide.

Samples for histological analysis were processed by commonly used methods.Whole brains were fixed in%10 formaline.

RESULTS

On the first day after the irradiation the animals were very lethargic. However, the apparent lack of gross evidence of any severe effect for several days was unusual. About the fifth to sixth day following exposure, weight loss and ruffled fur were observed in group one and by eight day some of them died. Daily mortality increased by 10^{th} to 14^{th} day then subsides. When the radiation increased to 7.5 GY somewhat different pattern of illness and death occurred. The animals in this group were severely injured by the day 3^{rd} to 4^{th}. Loss of weight were pronounced and by the fifth day some of them were died. There was a sharp peak of mortality. Non were survived beyond the 2^{nd} week. The animals which received the highest dose of irradiation were severely prostrated, very wet with sweat and by the second day some of them were already dead by the 3^{rd} day. All the rats in this group died in the 1^{st} week period.

Result of quantitative analysis of structural disorders in the central nervous system revealed radiation produced damages early after exposure which correspond to vascular responses and included foci of hemorrhages accompanied with severe vasogenic and cytotoxic edema (Fig. 1), on the first week after exposure in group three, rarefaction and necrosis was observed in the subcortical area of brain hemisphere (Fig. 2).The deteriorated regions were surrounded by gliosis, were predominantly located

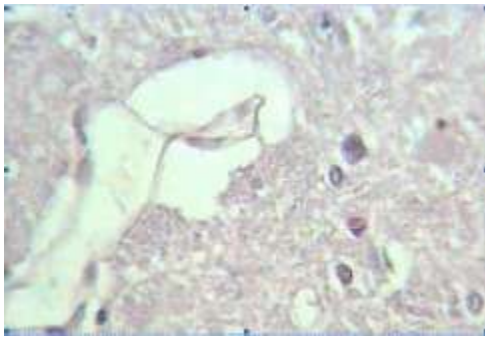

Fig. 1: Vasogenic edema in the brain of a rat in . Note the accumulation of fluid in the perivascular (Virchow - Robin) space (hematoxylin-eosin; original magnification & 400)

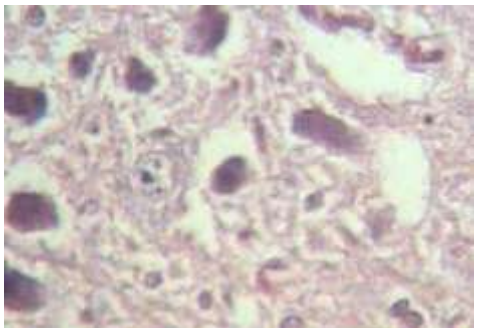

Fig. 2: Necrosis in the neurons. The cells have lost their nuclei and normal cell outline.(hematoxylin-eosin; original magnification & 400).

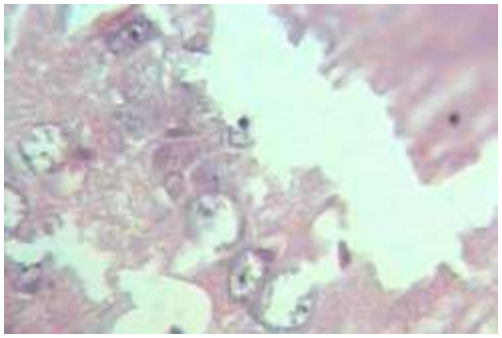

Fig. 3: Vacoules in the glial cells and neurons in the brain (hematoxylin-eosin; original magnification & 400).

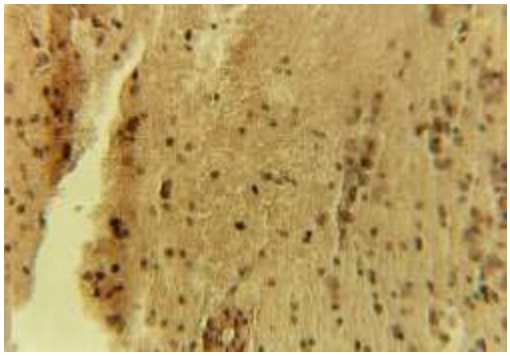

Fig. 4: Thickened vessel wall and a cystic cavity in the brain cortex (hematoxylin-eosin; original magnification & 250).

in the white matter of the medullary layer more on the white mater. Hemorrhages were visible either within the necrotic areas or were restricted to areas surrounding the cystic necrosis (Fig. 3).

The viable tissue around the necrotic areas showed only minor signs of glial inflammatory cell reaction. The blood vessels around the necrotic area were abnormally dilated with varying degrees of edema of adjacent tissue (Fig. 1). Occasionally, endothelial-cell nuclei were enlarged. Close to the blood vessels, hypertrophic and proliferating astrocytes with no mitotic figures. were detectable.

Irradiation at dosage of 7.5 Gy resulted in morphological changes of astrocytes in size within 1 month. Dilatation of vessels and capillary thickening were also observed (Fig. 4).

No sign of necrosis was visible 1 month after irradiation in animals exposed to 5 Gy, yet marginal morphologic alterations, such as slight tissue swelling and mild abnormalities of glial and neuronal architecture,were observed. In control group which did not received the irradiation no morphologic perturbation at all at this observation were exhibited.

DISCUSSION

The difficulty in obtaining histological evidence of radiation induced brain changes in patients who have undergone radiation therapy in brain is reflected in the infrequent availability of histological proof of these changes in humans [2,13,14].

In an organ such as the brain, different topographical regions may have varying susceptibility to ionizing radiation. Radiation induced lesions tend to occur more frequently in the cerebral brain white matter. The main findings in this study was the radiation necrosis in the cortex and subcortical area in the brain. There are controversial views as to relative importance of vascular theory versus the glial theory as the prime underlying element of pathogen-nesis of radiation necrosis [10,15]. Multiple studies implicated the loss of oligodendrocytes whether directly or indirectly as the primary cause of brain injuries.Oligodendrocyte associated with myelination may be damaged via radiation-induced apoptosis and depletion of oligodendrocytes may cause delay of demyelination [7,9,16]. As a result white matter tissue is more affected than gray matter tissue. Additionally there is loss of granular cells in the hipocaampus up to 3 months after brain irradiation. However, these data did not extend over a long period of time and is not clear from the current literature that recovery with these cells is possible. It was attempted, but were not able to obtain good tissue staining for oligodendrocytes, however, loss of these cells are evident through the massive proportion of necrotic areas and vacouls in the brain.

Van der Kogel [17] classified the brain tissue reaction to irradiation insult into, acute, early–delayed and delayed reactions. But the exact mechanism that lead to delayed injuries such as demyelination and white matter necrosis is still unclear [9,16,18].

Physiology of the normal function of the blood-brain barrier depends mainly on the tight junctions between endothelial cells. The vascular system, together with the blood-brain barrier, is believed to be the main target structure for development of delayed and acute radiation [13,19,20] effects. One of the most significant findings was cytotoxicity and in the early reactions. Radiation may have effects on fibrinolytic enzyme system with an absence of tissue plasminogen activator with an excess in urikinase plasminogen activator impacting tissue fibrinogen and extracellular proteolysis with subsequent cytotoxic edema and tissue necrosis. Whether immune–mediated cell mechanism may also contribute to radiation-induced neurotoxicity is unclear, but an autoimmune vasculitis has been postu-lated as a secondary host response to tissue damage [1, 8, 21]. However there is limited information about long term effects of radition on the endothelial cell Panagiotagos *et al.* [8] reported the endothelial cell numbers recover to near normal within 2 weeks.

Alterations of glial cells have only a minor effect on the blood-brain barrier [4,22,23].Our present structural and functional results are in accordance with study findings that show a strong correlation between functi-onal radiation effects and vascular alterations, which suggests vascular injury is a major factor that contributes to the pathogenesis of delayed radiation injury in normal tissues [12,24,25].

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