PATHOLOGICAL MECHANISMS OF THE PSYCHIATRIC COMPLICATIONS ASSOCIATED WITH RADIOThERAPY FOR BRAIN TUMORS

Abstract
The neoplasms of the central nervous system represent a frequent and heterogeneous disease group, with treatment implying a combination of surgical intervention with both chemotherapy and radiotherapy. Cerebral radiotherapy affects not only the tumor tissue but also the viable brain tissue, causing direct lesions to both the white matter and the gray matter and so leading to cognitive impairments, depressive and anxiety syndromes. The pathogenesis of psychiatric syndromes induced by radiotherapy is complex and not yet fully understood and the current review tries to summaries some of the possible pathogenic ways involved. Key words: radiotherapy, cognitive impairment, depressive syndrome

The neoplasms of the central nervous system make up a heterogeneous disease group, the treatment of which generally implies combining a surgical intervention with both chemotherapy and radiotherapy. Whole Brain Radiotherapy (WBRT) has been used as the primary non-surgical therapeutic modality for the treatment of brain tumors (1) and was due, in part, to the limited other chemotherapeutic options demonstrated to be efficacious. Many patients in whom control of brain disease is achieved with WBRT are surviving to experience the considerable neurocognitive sequelae and declines in quality of life that are associated with this treatment (2, 3, 4, 5). Despite the technological progress, cerebral radiotherapy also affects the viable tissue, causing direct lesions to both the white matter and the gray matter through inflammation, angiogenesis and cellular death. Depending on which healthy cerebral areas are irradiated (structures belonging to the limbic system and the cerebral system, the frontal lobes and the temporal lobes), the patients with cerebral tumors will frequently display cognitive disorders (functions like attention, short term memory, processing speed, learning, visual orientation and speech being the most frequently affected) (6, 7). Meyers et al (8) reported in a study including patients that had received radiotherapy 20 months to 20 years prior, that 80% of the patients displayed memory disorders, processing speed, learning, visual orientation, and speech being the most frequently affected (6, 7). Other frequent complications of cerebral radiotherapy include: ages older than 60, other therapeutic interventions (like chemotherapy) on cognitive function (10).

The acute effects occur within the first 48 hours to the first week and imply dizziness, headaches and nausea. The subacute effects may also be observed (17, 18). All these symptoms like seizures and an increase of intracranial pressure may also be observed (17, 18). All these cognitive disorders resulted from cerebral radiotherapy probably due to the specificity of the assessments (9) but other data from literature suggests an incidence of between 0 and 80%. The degree of neurocognitive decline in patients with brain tumors receiving radiotherapy can be confounded by the effects of tumor at presentation and other therapeutic interventions (like chemotherapy) on cognitive function (10).

Rezumat
Neoplasmele sistemului nervos central reprezinta un grup frecvent si heterogen de afecțiuni al caror tratament implica de obicei combinarea tehnicilor chirurgicale cu chimioterapia sau radioterapia. Radioterapia cerebraala nu afecteaza numai tesutul tumoral ci si tesutul cerebral viabil, determinand leziuni directe atat asupra substantei albe cat si cenusii si producand astfel deficit cognitive sau sindrome deprimative sau anxioase. Mecanismul patogenetic al sindromelor psihiatrice induse de radioterapie este unul complex si inca neinteles pe deplin iar acest articol incearca sa sumarizeze cateva din posibilele cauze patogene implicate. Cuvinte cheie: radioterapie, deficit cognitiv, sindrom depresiv

1 MD, PhDs, Coltea Hospital, UMF “Carol Davila”, Bucharest
2 MD, Floreasca Emergency Clinical Hospital, Bucharest
3 MD, CETTT “Sf. Stelian” Hospital, Bucharest
4 MD, PhD, Associate Professor, UMF “Carol Davila”, Bucharest
5 MD, PhD, Professor, UMF “Carol Davila”, Bucharest

Received April 27, 2017, Revised May 28, 2017; Accepted June 19, 2017

Corresponding author:
Mihaela Dumitrescu
psychiatric and neurological effects may lead to a poor quality of life as some studies may suggest (19, 20).

When the cells and stromal cells or the central nervous system are exposed to ionizing radiations, the neurons, neuroglia and blood vessels respond in a similar way to the cells and stromal cells other organs. Post-irradiation lesions are similar to the rest of the body and changes in function are comparable. Higher dosage of radiation can lead to immediate death of neurons, the activation of astrocytes and production of reactive gliosis (similar to the post irradiation peritoneal fibrosis). The irradiation of the oligodendrocytes affects the formation and maintenance of the myelin sheath, that can lead to demyelination and affect the transmission of the nerve impulse. The blood-brain barrier can be affected and can lead to the occurrence of cerebral edema, the consequences of which can be disastrous (comparable to the emergence of pulmonary hyaline membrane disease in lungs prior exposed to ionizing irradiation). Both large blood vessels and the capillaries are affected by lesions similar to the rest of the body but given the lower resistance to ischemia of the cerebral tissue the toxic effects are of greater importance. Consequent to the action of ionizing radiation on a cerebral level several types of lesions can be observed: demyelination, proliferative and degenerative glial reactions, loss of endothelial cells and occlusion of the capillaries. All these changes are as a result to complex alterations that took place in different cerebral functional compartments: damage to vascular structures, the disappearance of the precursors of mature astrocytes and oligodendrocytes, the disappearance of the neural stem cells from the hippocampus, cerebellum and cortex, generalized alterations to the expression of the cytokines. To sum up the facts, there are 3 targets for the radiations on the cerebral level: the neurons, the glial cells and the vascularization, but the distinction is somewhat arbitrary given that there is significant interaction in between these components.

Effects on the neurons
Certain studies prove the fact that radiation can induce the apoptosis of neurons in the case of newly born animals (21) although in the case of adult animals the observed effects weren't similar (22), confirming the fact that the neurotoxicity of radiation does not have direct damage to neurons as an underlying factor. 

Vascular toxicity
Vascular alteration is important in the development of post-irradiation complications and structural alterations at the cerebral level (23). The first effects of the radiation on a capillary level are the detachment of the endothelium, cytoplasmic vacuolization, increases in nuclear volume, changes that determine the development of the initial edema. The endothelial cells become hypertrophied causing a reorganization of the f-actin filaments. Eissner and collaborators show that endothelial apoptosis can be achieved by generating intracellular ceramides or the adhesion of the irradiated leukocytes that can trigger the apoptosis thought TNF (24). The endothelium is progressively damaged for weeks to months, which leads continuously to the aggregation of irradiated platelets and the formation of blood clots, until the vessels become partially or fully thrombosed which in turn leads to the hypoperfusion of cerebral tissue. At the same time an abnormal proliferation of the endothelium as well as the thickening of the basement membrane and the replacement of the lumen with collagen deposits can be observed (?). The cellular mechanisms involved in the pathogenesis of vascular toxicity induced by radiation include and increase in the production or various adhesion molecules that mediates the aggregation of leukocytes on the vascular walls, like E-selectin and ICAM-1 (25). Endothelial cells display a decrease in enzymatic activity: alkaline phosphatase, the enzyme responsible for the conversion of angiotensin. The increase of permeability for different molecules, hyper coagulation and increased aggregation of thrombocytes because of the increase in the production of the von Willebrand factor and a decrease of the plasminogen activators, consequent in an inefficient fibrinolysis, can be observed. Endothelial cells, of course, have defense mechanisms against the effects of radiation, they consist of reactive oxygen species like glutathione or superoxide dismutase (26).

In a in vitro study was observed that the lethal dose or radiation for the endothelial cells ranges between 100 and 200 cGy (27). The in vivo doses what would have a similar effect are much higher. Sub-lethal doses of radiation affect the morphology and different functions of the endothelial cells.

Gial cells and demyelination
Many of the effects radiation has on the central nervous system can be explained by disorders in the transmission of nerve impulse which originate from demyelination. Oligodendrocytes play a key role in the demyelination produced by radiation. Both oligodendrocytes, that play a role in the formation of the myelin sheath and astrocytes, that contribute to the transmission of electric potential through the nodes of Ranvier have a common precursor, namely the O2A cells (type 2 oligodendrocyte-astrocyte precursor). Radiation can affect the O2A cells directly, thus decreasing their numbers and reducing the possibility of regeneration for both the oligodendrocytes and astrocytes. The radiation also has negative effects on adult oligodendrocytes, reducing their number and thus creating the need for additional production of new ones from the O2A cells. Oligodendrocytes can be affected by cytokines like TNF alpha, the production of which can be simulated by radiation (28). The theory behind the involvement of oligodendrocytes and O2A cells in the occurrence of post-irradiation demyelination lesions is not completely explained, but there is sufficient proof from animal studies (29, 30, 31).

An important cerebral area that is affected after radiation is the hippocampus which remains mitotically active in adults. Studies have shown that the cells from this area are capable of differentiating between neuron and neuroglia and of migrating long distances in order to contribute to the reparatory processes after the radiation therapy (32). It is demonstrated the hippocampus involvement in the pathogenesis of depressive disorder and cognitive impairment, and radiotherapy techniques sparing this region could improve the post treatment status of patients receiving brain radiotherapy.

Radiation induced apoptosis and gene expression
The induction of apoptosis in the case of different cerebral cellular compartments is the basis of the toxicity of radiation. Two major mechanisms to induce apoptosis on a cerebral level:

- the first mechanism consists of the activation of
apoptosis by the ligand family of TNF alpha, CD95-L and TRAIL-R1 and TRAIL-R2 via caspase 8

• the second apoptotic mechanism concerns direct toxicity for DNA, especially the mitochondrial DNA which determines the activation of the caspase system (33) Simultaneous to the induction of apoptosis, the activation of certain gene expression seems to play a major role in the cerebral toxicity induced by ionizing radiation. Among the genes with an increased expression because of the radiation the most important ones seem to be proinflammatory cytokines (TNF alpha, INF gamma) and the adhesion molecules (ICAM).

Radiation therapy has an important role in the management of brain tumors and could be considered a targeted therapy as it remains the ‘go to’ modality for the treatment of most brain tumors, particularly at the time of initial diagnosis. However, these interventions are responsible for well recognized and substantial adverse events in some cases (34). Neurotoxicity that arises from cancer treatment and especially from radiotherapy has been widely recognized and could limit the course of treatment (35). Common adverse effects of cancer treatment include cognitive dysfunction, depressive and anxiety syndromes which result from direct damage to the nervous cells and their surrounding microenvironment. The complete pathogenesis of psychiatric syndromes induces by radiotherapy is complex and not yet fully understood and effective strategies to minimize these problems would be of great advantage to the patients with brain tumors.

References:

Conflict of interest: none declared
Financial support: none declared