



Effects of Ionizing Radiation and their Potential Risk on the Brain: A Review

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Abstract

The brain is considered as one of the most radioresistant organ in the body. However, more and more studies start to question this resistance. The aim of this paper is to briefly review the current available data regarding the impact of ionizing radiation on the brain with a focus on epidemiological/clinical studies.

Keywords: Cognition, Irradiation-Induced Brain, Radiation Exposure, Radiation-Induced Brain Damage, Radiation-Induced Brain Injury

1. Introduction

All living beings are exposed with various degrees to ionizing radiation. The source of these radiations may be natural (cosmic or terrestrial sources) or caused by human activity (military or peaceful purposes).

In the recent decades, the medical use of ionizing radiation has rapidly evolved all over the world, it became a key tool with its wide range of applications in diagnosis and treatment of various diseases. The Radiological Society of North America (RSNA) estimated that around 3.6 billion Medical procedure using ionizing radiation are performed annually worldwide, including nuclear medicine examinations¹.

These procedures cause a significant radiation exposure to patients with an annual cumulative dose estimated to 3.0 milliSievert (mSv) per capita in developed countries².

In addition to that, approximately 30 million medical workers are unavoidably exposed to these radiations, among them professionals in radiology and nuclear medicine, but also orthopedists, interventional cardiologists, dentists and veterinarians^{1,2}.

In the history of radiation exposure, physicians and technicians in radiology were among the earliest populations professionally exposed. Several deaths have been reported among them by the beginning of the last century when the causal relationship had not yet been clarified³. Between the twenties and the forties, epidemiological evidence from different American and European studies showed a high frequency of leukemia and other malignancies among these medical workers, then the use of the atomic bomb in World War II (WW II) demonstrated the deleterious and destructive effects of high dose radiations, it also permitted a better understanding of the risks related to ionizing radiation with a clear dose-effect relationship of high dose radiations creating thus the main source of information regarding the exposure of various organs³⁻⁶.

Our understanding of the mechanisms responsible for these harmful effects began in the beginning of the 20th century the first laws explaining action of Ionizing Radiation (IR) on living things called "radiation biology" were published in 1906 by Bérgonié et Tribondeau then refined in 1968 by Rubin and Casarett. These laws establish a strong relationship between radio sensitivity and cell proliferation⁷.

Unlike gonads, the central nervous system is composed essentially by fixed postmitotic cells (differentiated non dividing cells) thus considered as the most radioresistant tissue among others such as muscles, erythrocytes and spermatozoa⁶. However, many recent studies start to question brain radio resistance by reporting neurobehavioral and cognitive effects in individuals exposed to IR. Yet, data remain scarce and statistically limited thus limiting a better quantification of its detriment on this important organ.

Aim of the study: In order to draw-up an inventory of the exiting data regarding the impact of IR on the brain, this paper briefly reviews the current available data on the subject with a focus on epidemiological/clinical studies.

2. Materials and Methods

We searched the 'Pubmed' database (MEDLINE) using search terms including among others: irradiation; radiation exposure; irradiation-induced brain; radiation-induced brain injury; radiation-induced brain damage; cognition; cognitive decline; neurobehavioral dysfunction; neurotoxicity with no restriction regarding publication date, location or language. The study radiation induced carcinogenesis and studies referring to species other than humans. A section of studies was then acquired and reviewed, and sometimes their bibliographies pursued for further clarifications and details.

3. Results

After an exhaustive research using the MESH words mentioned above, this study selected:

- Guidelines from international organizations: International Commission on Radiological Protection (ICRP), United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).
- Books: teratology in the twentieth century plus ten by Springer Science/essential physics of medical imaging by Lippincott Williams and Wilkins.
- Reviews evaluating the risk of high dose and/or low dose IR exposure in the human.
- Studies evaluating cognitive functions/behavioral impairments in patients exposed to radiations (atomic bomb/radiotherapy/occupational exposure).

4. Discussion

4.1 International Radiation Protection Regulations

As its name suggests, radiation protection is a field with the aim of protecting people from risks caused by the exposure to IR on health. Two main categories of risks exist:

1. The well-known high doses effects or "deterministic effects" which appear conclusively beyond a well determined threshold and are often of an acute nature, their manifestation reflects cell death or their malfunction (conventionally indicated by the Gray unit or Gy) this is a preventable effect only seen in exceptional circumstances (after nuclear accidents/ bombing or as an intended effect in therapy).
2. The statistical risk increase of cancers and heritable disease, what is now termed the stochastic/probabilistic effect, this is mainly caused by low radiation doses but may also be caused by high doses (Uses the Sievert unit or Sv)³.

In order to avoid these harmful health effects, an international commission was created in 1928 and took the name of the International Commission on Radiology Protection (ICRP) in 1950. It's an independent nonprofit making organization working closely with different international agencies such as the World Health Organization (WHO) and the International Atomic Energy Agency (IAEA). Its mission is to provide recommendations and advices on radiological protection, firstly in 1928 by restricting the working hours with radiation sources in order to reduce the duration of exposure. Decades later, the commission introduced a system of safe doses based on the three principles of justification, optimization of protection and dose limitations or threshold doses. It introduced also the concept of categories of exposure, occupational exposure/medical exposure of patients/public exposure, each one with its own regulations. The guidelines are permanently reviewed and updated taking in to account advances in scientific knowledge and available epidemiological evidences³.

In order to ensure that the emergence of stochastic effects is kept under the recommended levels, the commission introduced the "protection quantities" based on the average absorbed dose taking into account radiation characteristics (type of radiation, energy) attributing to each type of radiation its radiation weighting factor

(W_R) and to each tissue its tissue weighting factor (W_T) reflecting its vulnerability to radiations and its relative contribution to the total health determinant caused by uniform body irradiation³.

4.2 Questioning of the Brain Radio-Resistance

The central nervous system was for a long time considered as resistant to ionizing radiation. The first studies were based on survivors from Hiroshima and Nagasaki after WW II, radiation accidents and lately from patients receiving radiotherapy. Neurological symptoms do appear only after high and acute total dose exposition (>30 Gy), far ahead of hematological (>4 Gy) and gastrointestinal (10 Gy) thresholds.

The ICPR guidelines didn't attribute a tissue weighting factor (W_T) to the brain in ICPR 26 and 60 until 2007 with its 103 guidelines which were the first to consider the brain as an organ which may be vulnerable to ionizing radiations by reassessing its W_T to 0,01. This relative biological impact remains relatively low compared to other tissues such as lungs, colon, breasts ($W_T = 0,12$), esophagus and liver ($W_T = 0,04$) and take into consideration only carcinogenic effects.

4.3 The Brain Radiobiology

On the biological and cellular level, the impact of ionizing radiation on the brain is relatively complex with multiple interactions and intricate mechanisms. Radiation induced injury is the consequence of the interaction between radiations and atoms and molecules inducing the production of Reactive Oxygen Species (ROS) whose main target is nucleic acids⁸. On the cellular level alterations are seen in the: 1. endothelium altering the neurovascular permeability, 2. white blood cells with the activation of microglia causing neuroinflammation and prothrombotic activation, and 3. the apoptosis of oligodendrocytes and neural stem cells causing among others myelin degeneration, white matter integrity alteration and neurogenesis dysregulation^{9,10}.

5. Clinical Effects of High dose Exposition on the Brain

Effects of exposition to high dose IR are labelled as deterministic given their early and acute occurrence above a threshold. it's caused by the significant number of injured/

killed cells leading to tissue or organ dysfunctions with an alteration of cell kinetics and architecture both the incidence and the severity of the symptoms are correlated to the intensity of the radiation dose but also by its rate, fractioning and quality^{3,11,12}.

There is a relative abundance of epidemiological data regarding the effects of high dose IR on the brain.

The first studies evaluated the impact of IR on a developing brain. Indeed, children born to women exposed during their pregnancy to pelvic radiation showed an impact on the central nervous system with a critical period between 8 and 25 weeks inducing clinically small head sizes with mental retardation and low intelligence quotients^{3,12,13}. It's explained by the impact on cell proliferation including neurones that not only proliferate during this period but migrate to specific sites. It involves also glial cells alteration causing demyelination.

Many studies evaluated people who survived the atomic bomber in Japan in WW II and nuclear incidents^{14,15}. Data show that a whole-body acute exposition to 4 Gy (Gray) leads to death of a population within 30 days. Cerebro vascular syndrome appears only after very high doses 20–100 Gy leading to cerebral edema, severe cerebral blood microcirculation disorders causing intra-cerebral hemorrhage and acute motor weakness due to excitotoxicity. It may also lead to blood brain barrier and blood cerebrospinal fluid barrier interruptions causing metabolic and ischemic disorders. The survival time is about days to hours³.

Other studies evaluated the long-term impact of nonlethal IR doses on Chernobyl "liquidators" (workers in the restricted 30 km zone after the nuclear reactor incident), and found a correlation between IR exposition and schizophrenia-like disorders and neurodegenerative diseases such as Alzheimer disease¹⁶. However, IR may be only a potential cause of these neurological disorders among others such as environmental mental stress, chemical or physical contaminants and sleep deprivation during shifts^{17,18}.

Current studies rely on data from patients treated with radiation therapy which, unlike acute irradiations, IR dose is fractioned resulting in repopulation and repair of cell sub-lethal damages thus increasing the irradiation tolerance.

Other than the well documented leuco-encephalopathy, radiation necrosis, radiation induced vasculopathy and optic neuropathy^{19,20}. Douw et al. assessed the impact of radiotherapy on the cognition in patients with low grade glioma and showed signs of progressive decline in attention functioning even in patients who received a fraction dose

less than 2 Gy, a fraction regarded so far as safe (focal radiotherapy/2 cm margin around the lesion/mean total dose 56 Gy/1,6 to 2,5 Gy per fraction)²¹.

Other studies showed the same results by finding a high correlation between IR exposition and cognitive/neurobehavioral effects such as apathy, disinhibition, dysthymia and executive functions impairments^{22,23}.

In the population of patients with brain tumors treated by radiotherapy, some studies evaluated the late consequences of brain irradiation on cognitive functions and found that more than 50% of patients exhibited a progressive and disabling dysfunctions including learning, memory, processing speed, attention and executive functions².

However, the disease itself (brain tumours) and additional treatments such as antiepileptic drugs may lead to similar symptoms which may raise the risk of biased results².

In this regard, McDowell et al. excluded brain tumours and evaluated the effects of IR only in treated patients with head and neck cancer using Intensity –Modulated Radiotherapy (IMRT) which is known to significantly reduce the dose delivered to nearby healthy tissues. The results showed that some patients experienced sensations of electric shocks mainly explained by the temporary demyelination of sensory neurons, others showed higher anxiety and depression scores as well as other behavior dysfunctions related to frontal lobe (apathy, disinhibition and executive dysfunction)²³⁻²⁵.

6. Clinical Effects of Low dose Exposition on the Brain

The impact of low dose IR on the CNS is still unclear. One of the first studies evaluating this impact was published in the fifties by Baverstock et al. which assessed the frontal lobe functioning in four cases who received during a radiation accident doses ranging from 0,12 to 1,9 Gy. They use the Halsted test battery for frontal lobe functional deficits and did not find any alteration on day 1,4 and one year after the exposition to mixed radiations (neutrons and gamma)²⁶.

Studies published by Yamada et al. from atomic bomb survivors below this threshold did not find any difference of dementia incidence between groups exposed to doses less than 5m Gy, between 5 m Gy and 500 m Gy and greater 500 m Gy^{16,27-29}.

Some epidemiological studies were based on death registration data. They have thereby a common bias of

using death certificates data for a degenerative disease which does not lead necessarily to death. Based on death registers from 22 American states, the study of Park et al. didn't show a link between professional exposures to IR and cognitive disorders, particularly in radiology technologists³⁰.

The nested case-control study published by Sibley et al. provided an association between radiation exposure and the likelihood of dying from dementia in workers from twelve American nuclear weapon plants. The study compared the cases of death from dementia in female workers with a group of controls. Statistical analysis showed a significant dose – response relationship in both maximum annual (intervals between 0,0–4, 9 mSv, 5, 0–9, 9 mSv, 10, 0–24, 9 mSv and 25, 0 – 49, 9 mSv) and total lifetime radiation doses (intervals between 0, 0 – 9, 9 mSv, 10, 0 – 24, 9 mSv and 25, 0 -49, 9 mSv and > 50 mSv). However, several bias need to be considered, the small number of cases (168 cases), and the lack of data regarding the quantification of radiation exposure³¹.

Lehrer et al. examined the possible relationship between Alzheimer disease and natural IR exposition in US states and found a high correlation between Alzheimer disease and background IR, especially Radon background (222 Rn). He explained these results by a high exposition of the rhinencephalon and hippocampus to this radioactive gas after its inhalation. Plus, Radon and its daughters may also pass the blood – brain – barrier. Damage would accumulate over time making also age to be a powerful risk factor³². Other cohort studies evaluated health outcome medical workers exposed to IR^{11,33-36} but to our knowledge none of them focused on its impact on the brain.

In summary, deterministic effects on the brain are well known and documented, but data regarding low dose IR effects are still scarce. More epidemiological and clinical studies remain to be done in order to investigate the potential effect of this exposure on the brain in order to assess their risk among both workers and patients.

7. Clinical Significance

This review draws up an inventory of the existing data regarding the impact of IR on the brain with a focus on epidemiological/clinical studies thus assessing the risk of this type exposure.

8. References

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