PSYCHIATRIC EFFECTS OF IONIZING RADIATION

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Abstract

Radiation exposure leads to an increased risk for cancer and also atherosclerotic, cardiovascular, cerebro-vascular and neurodegenerative effects.

Different data would indicate that radiation-induced neurodegeneration is a multifactorial process involving several all types with oxidatively-stressed mitochondria being a recurring element.

With the present paper we aim to present a comprehensive review on brain effects of radiation exposure, with a special focus on their possible role in the pathophysiology of different psychiatric disorders.

Key words: ionizing radiation, neurogenesis, hippocampus, brain areas, psychiatric disorders

Declaration of interest: none

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Introduction

Ionizing radiation (IR) is a radiation with enough energy so that during an interaction with an atom, it can remove tightly bound electrons from the orbit of an atom, causing the atom to become charged or ionized. The fact that these radiations are ionizing allows them to be detected and discriminated from other forms of radiation (such as infra-red or radiowaves). Ionizing radiation is present in three varieties: α (alpha) particles, β (beta) particles, and γ (gamma) rays. All these forms of radiation are energetic enough to remove electrons from atoms. Alpha particles are strongly ionizing, but can be stopped by paper or skin. They have a strong positive charge (+2) and a mass of 4. One alpha particle can ionize 10,000 atoms. However, because it puts all its energy into ionizing others, it very quickly runs out of energy itself. Hence, alpha particles cannot penetrate through much. Beta particles are electrons, but they are called beta particles to identify that they come from the nucleus of the atom; these particles are also strongly ionizing (perhaps 1 beta particle will cause 100 ionizations). Gamma rays are very poor at ionizing (about 1 to 1), but they are very difficult to stop and are very penetrating. Therefore, gamma emission accompanies most emissions of beta or alpha particles. In eukaryotic cells, ionizing radiation induces damages to proteins, lipids and DNA, directly or indirectly, as a result of free radical formation. Cell signaling events in response to IR depend on environmental conditions occurring during DNA repair, besides genetic and physiological features of the biological systems (United Nations Scientific Committee on the Effects of Atomic Radiation 2008; Food and Drug Administration 2010).

Medical radiation from x-rays and nuclear medicine is the largest manmade source of radiation exposure in Western countries, accounting for a mean effective dose of 3.0 mSv per capita per year, similar to the radiologic risk of 150 chest x-rays (Picano 2004; President’s Cancer Panel 2010). About 30 million workers are professionally exposed to radiation, and of these the interventional fluoroscopists (cardiologists and radiologists) are amongst the most exposed. In fact, their annual exposure is equivalent to 5 mSv per year which would lead to a projected lifetime attributable excess cancer risk of 1 in 100 (United Nations Scientific Committee on the Effects of Atomic Radiation 2008; Venneri et al. 2009). This explains the increasing interest of scientific community on cancer and non-cancer, including brain effects of radiation exposure. The effects can be clustered in low dose effects (<100 mSv), generally reached with acute medical diagnostic exposures; moderate dose (100-1000 mSv), reached with chronic repetitive or cumulative professional fractionated exposures, for instance in interventional cardiologists and radiologists; and, finally, high dose (>1 Sv or 1 Gy) exposures, of particular interest in radiotherapy (Annals of the Institute for International Research on Criminal Policy 2012). Currently, the majority of the data are those regarding radiotherapy dose range, while just a few information is available on the moderate-to-low dose range, that probably is where we need them most (Picano and Vano 2011). Therefore, there is a great need for exploring what and if low/moderate doses may provoke any dangerous effect, especially on the brain which is now recognized one of the main dose-limiting organs in radiotherapy (Tofilon and Fike 2000). Given the high number of
Psychiatric effects of high doses of IR

In the studies evaluating the effects of total cranial irradiation on cognition and emotions, IR was demonstrated to provoke cognitive deficits in exposed individuals, especially during childhood and adolescence. However, the relatively short follow-up time (<10 years) did not allow to evaluate the possible association between IR and dementia.

In a retrospective study involving the general population of Rochester, no association was found between radiation therapy (RT) and Alzheimer’s disease (AD) (Peper et al. 2000). Another US study carried out in subjects exposed to whole brain RT reported an incidence of dementia ranging between 1.9 and 5.1%, not different from that of the general population (DeAngelis et al. 1989).

In the few studies exploring the possible occurrence of depression after cranial irradiation, no relationship was detected (Roman and Sperduto 1995, Armstrong et al. 2002). In the early-delayed phase, the cranial irradiation-related cognitive changes were not accompanied by depression (Armstrong et al. 1995, Armstrong et al. 2000, Armstrong et al. 2002). However, depression seemed to occur between the 4th and 6th year after the treatment, possibly related to fatigue and cognitive impairment (Armstrong et al. 2002). In any case, convergent data from animal studies showed that cranial irradiation can provoke relevant damage of the hippocampal areas which are crucial for neuronal plasticity and, as such, for memory, learning, emotions and stress response (Monje et al. 2002, Hartung et al. 2011).

Interestingly, in the last decade, different psychiatric disorders, including depression, bipolar disorder and schizophrenia, have been hypothesized to be related in some ways to neurogenesis disturbances, especially at hippocampal level. Even several psychotropic compounds, specifically antidepressants and mood stabilizers, would exert part of their effects by improving the survival of selected neurons and neuronal plasticity in the hippocampus (Duman et al. 1997, Popoli et al. 2002, Manji et al. 2003, Schumacher et al. 2005). Therefore, it is plausible that the reduction of neurogenesis could predispose vulnerable individuals to the onset of psychiatric disorders and negatively affect the course of their symptoms and treatment outcome. This could be especially true for schizophrenia which is now considered a multifactorial neurodegenerative illness, where neurobiological genetic predisposition can be provoked by environmental stressors (such as IR), while resulting in the occurrence of the disorder.

There are evidence of an increased incidence of schizophrenia spectrum disorders following exposure to atomic bombing radiation, or environment with high natural IR level (Loganovsky et al. 2005). In fact, a significant enhanced prevalence of schizophrenia has been reported in the survivors in Nagasaki (Nakane and Ohta 1986). The prevalence of schizophrenia was about 6% significantly higher than that found in the general population where it is estimated to be about 1% (Shore et al. 1986, Fuller Torrey 1995). Unfortunately, this study has several methodological limitations due to the fact that the Life Span Study, started by the radiation effects research foundation (RERF) in Japan did not include data on severe mental disorders. In addition, the findings were obtained combining the schizophrenia register of the Department of Neuropsychiatry, University School of Medicine of Nagasaki, with the LSS register. However, the schizophrenia register had been operative only since 1960 and it was not possible to calculate annual inception rates back to the bombing in 1945 (Iwata et al. 2008).

As far as Chernobyl survivors are concerned, there was a significant increase in the incidence of schizophrenia in the exclusion zone area starting from the 1990: 5.4 per 10,000 in the exclusion zone personnel versus 1.1 per 10,000 in Ukraine in 1990 (Loganovsky et al. 2000). It was, thus, proposed that the development of schizophrenia spectrum disorders in Chernobyl survivors was the consequence of a radiation-induced left fronto-temporal limbic dysfunction. Further, prenatally irradiated children after the Chernobyl accident were found to be at higher risk for schizophrenia (Nyagu et al. 1998).

Further, the incidence of schizophrenia was found to be higher in people living in the region of the Semipalatinsk nuclear weapon testing area in Kazakhstan. In fact, about 29% of patients with mental disorders living in the area were affected by schizophrenia and, amongst those, 42.3% were born before the first nuclear test of India that have high natural background radiation (Loganovsky et al. 2005). However, in a recent study evaluating the possible association between exposure to IR and schizophrenia, a group of more than 10,000 subjects exposed to head irradiation during childhood for treatment of tinea capitis did not show a higher incidence of the disorder, in comparison with two matched groups that had not been exposed to IR (Sadetzki et al. 2011).

In any case, data are really few and there is a great need of further studies to better understand the possible relation between IR, in particular of low to moderate doses, and different psychiatric disorders.

Psychiatric effects of low-to-moderate doses of IR

Occupational exposure to radiation was associated with death from dementia only in nuclear weapons workers, but not in radiology technicians (Sibley et al. 2003, Park et al. 2005). Further, the studies evaluating the incidence of dementia amongst atomic-bomb survivors did not find any associations (Yamada et al. 1999).

The studies on occupational or accidental exposures to IR are of great potential interest, but the evidence is limited and conflicting. The available data come from Hiroshima and Nagasaki atomic bomb survivors, Chernobyl blast, nuclear power plant workers and workers in medical fields (biologists, radiology technicians, radiologists and imaging practitioners, veterinarians). There are basically two different models of exposure: relatively high doses (> 4 Gy) over a relatively brief period of time, and relatively low doses (from 5 mGy up to < .5 Gy) over a much longer period of time. Yamada et al. 1999 reported no relationship between radiation exposure (< 4 Gy) and dementia in 2286 ageing atomic bomb survivors, with no difference
Psychiatric effects of ionizing radiation

Pathophysiology

The IR-related brain injury does not occur as a single, immediate event. It is considered a dynamic and multiphasic process occurring over time, characterized by pathological changes of vessels and myelin, resulting in vascular damage, white matter injury and coagulation necrosis (Calvo et al. 1988, Reinhold et al. 1990, Van Der Maazen et al. 1993, Hopewell and Van Der Kogel 1999, Tofilon and Fike 2000, Belka et al. 2001, Brown et al. 2007). In terms of pathophysiology, some findings showed that IR can lead to neuronal death (Enokido et al. 1996, Gobbel et al. 1998). Moreover, in vivo studies, carried out in animals, reported significant brain damage following IR. Histological changes, as well as cognitive functions, were investigated in the brain of 20 Fischer 344 rats aged 6 months treated with whole brain irradiation. In parallel to cognitive functions impairment, as revealed by the water maze task and the passive avoidance task, a relevant brain damage was reported, in particular demyelination, in some cases accompanied by necrosis in the corpus callosum and in the hippocampus.

The brain areas without necrosis were, however, characterized by decreased myelin basic proteins, alterations of neurofilaments and increased glial fibrillary acidic proteins with gliosis. These histological alterations of the brain structures after IR were similar to those found in neurodegenerative conditions such as Alzheimer’s disease,Binswanger’s disease and multiple sclerosis (Akiyama et al. 2001).

The occurrence of neuroinflammation has been found to be a significant component of the brain response to IR (Tofilon and Fike 2000, Monje and Palmer 2003). In fact, an increased number of activated CD68-expressing microglia has been reported after IR, so that it has been hypothesized that this might contribute to the alteration of the neurogenesis and to the hippocampal damage often described in animal models. The hippocampal granule cell layer, which are those capable to regenerate, has been found to be injured by RT, even at lower doses than those believed to damage glial cells or neurons (Monje 2002, Monje and Palmer 2003, Hartung et al. 2011). There is now convincing evidence that inhibition of adult neurogenesis in the dentate gyrus of the hippocampus affects learning and memory. In particular, the memory linking past events to the context seems to be very sensitive to a reduction of the neurogenesis (Winocur et al. 2006, Wojtowicz et al. 2008, Hernandez-Rabaza et al. 2009). In some studies, the negative effect of RT on hippocampal neurogenesis was irreversible (Wojtowicz 2006), while in others a recovery was observed, possibly related to the replication of the neural precursors (Monje et al. 2003, Rola et al. 2004, Ben Abdallah et al. 2007).

Significant increase in the incidence of cerebrovascular disease have been demonstrated in a cohort study of nuclear workers employed at the Mayak Production Association (Mayak PA), among workers who received cumulative doses higher than 0.2 Gy, compared with those who received <0.2 Gy (Azizova et al. 2011). This study provides evidence for the harmful effects of chronic low dose IR on the site of cerebrovascular system and not directly on cognition. There is also increasing evidence that cerebrovascular dysfunctions may be a relevant pathogenic factor in Alzheimer’s (Kurata et al. 2011, Tong et al. 2012, Viticchi et al. 2012). There are indications that vascular dysfunction leads to neurodegeneration and might be involved in cerebrovascular disease (CVD) such as cerebral beta-amyloidosis and cerebral amyloid
neurodegeneration in other conditions as PD may be a consequence of histological alterations due to chronic local inflammation after IR (Knott et al. 2000, Mirza et al. 2000, McGeer and McGeer 2004, Mrak and Griffin 2007). It has been suggested that oxidative stress is involved in PD progression, as increased levels of reactive oxygen species (ROS) have been shown to damage target neuronal cells (Hirsch 1993, Jenner 1998).

Microglia activation has been shown after local whole brain irradiation (5 Gy—X-rays) of mice (Rola et al. 2004). As a result microglias can produce and release large numbers of superoxide ions into the surroundings, contributing to increased levels of ROS (McGeer and McGeer 2004). Young mice exposed to whole brain irradiation showed that low doses of IR induced neuroinflammation in the hippocampus which was associated with a decrease in cognitive functions via reduced hippocampal neurogenesis (Rola et al. 2008). It is demonstrated that microglia activation and decreased hippocampal neurogenesis were directly proportional to the radiation dose.

The dopaminergic neurons are more vulnerable to oxidative stress compared with other brain structures. This is attributed to their low intracellular levels of antioxidants and elevated rate of oxygen consumption and calcium metabolism leading to higher ROS levels (Licker et al. 2009). It is postulated that dopamine metabolism and dysfunctions of mitochondria are themselves the causal factors for the elevated ROS levels seen in PD (Greenamyre and Hastings 2004, Licker et al. 2009).

It seems more plausible that the shift in the metabolism of surviving neurons to compensate dopamine loss and, thereby increase dopamine level (Elsworth and Roth 1997a, b) may contribute to mitochondrial defects and ROS increase during PD progression.

It is known that low doses of IR may cause immediate and persistent impairment of cardiac mitochondria. Complexes I and III being the main targets (Azimzadeh et al. 2011, Barjaktarovic et al. 2011). The mechanism of radiation-induced mitochondrial dysfunction both in the heart and brain is not completely understood. Ionizing radiation may directly interact with mitochondrial DNA (mtDNA) inducing mutations and deletions or indirectly through the formation of reactive hydroxyl radicals (Prithivirajasingh et al. 2004).

It is noteworthy that intact mitochondrial dynamics (fission, fusion, migration) are essential for neurotransmission, synaptic maintenance and neuronal survival (Bueler 2009). Disturbances of mitochondrial activity may lead to neurodegeneration in PD (Arduino et al. 2011). Impairment of mitochondrial dynamics happens early in the development of PD (Bueler 2009).

Taken together, mitochondria may not only play a key role in PD, but also in AD. This stresses the multifactorial role of mitochondria in the different cellular actions within the brain. A generalised depression of the mitochondrial electron transport chain activity has been observed in AD patients (Parker et al. 1994). Increased oxidative stress found in the AD (Butterfield et al. 2007) may result from oxidative phosphorylation defects; there is evidence that Complex I defects in particular may play an important role in the AD physiology (Eckert et al. 2010).

The model suggests that mitochondria play a central role in the radiation response followed by neuroinflammation and oxidative stress. Subsequent cellular effects lie in the reduction in neurogenesis and cerebrovasculature followed by neurodegeneration.

Conclusions

According to Annals of the Institute for International Research on Criminal Policy (2012), “The adult brain shows subtle effects at doses around 10 Gy and clear volume effects are discernable. Low dose irradiation (1-2 Gy) to the developing brain of children can cause long-term cognitive and behavioral deficits that may predispose to subsequent psychiatric symptoms and/or disorders, detected in adult life after exposure to doses >100 mGy before 18 months”. The crucial point is that, with no doubt, we need more data, especially outside the RT model, as well as in the low-to-moderate dose range. This is particularly relevant for both the scientific and social side due to the high number of patients and professionals involved, taking into account also that the IR dose of the side of IR is magnified by the relative lack of awareness by doctors and patients of doses and effects of diagnostic IR (Malone et al. 2011). In particular, a challenging model is represented by contemporary interventional cardiologists and radiologists, who may receive a whole body exposure after a professional lifetime around 100 to 200 mSv and a peak dose in the range of 1 to 3 Gy, falling well within the range of possible psychological and psychiatric effects. In studying this population of catherization laboratory professionals, we also need to be aware of the substantial limitations of the epidemiological approach, which requires very large populations followed-up for decades to detect clinically overt risks that can be even of moderate entity (Land 1980). Rather, as suggested by United Nations Scientific Committee on the Effects of Atomic Radiation (2008), we should focus on subclinical endpoints, as well as biomarkers, since this information is more likely to lead to insight. The ideal biomarker is a proximal sign of disease and a long-term predictor of clinical events. In case of psychological disease, the brain-derived neurotrophic factor is directly linked to hippocampal neurogenesis and is reduced in pre-depressive and degenerative conditions (Piccinni et al. 2008, 2008b, 2009; Zuccato and Cattaneo 2009). In Italy, this approach will be used in the Healthy Cath Lab study, promoted by the Italian National Research Council with endorsement of Italian Society of Invasive Cardiologist, and designed by interventional cardiologists for interventional cardiologists. Similar studies are being organized in US and sponsored by National Institute of Health and National Cancer Society (Food and Drug Administration 2010, President’s Cancer Panel 2010). These studies will hopefully produce in the forthcoming years the necessary evidence-base required to answer the unresolved issue of the psychiatric effects of low-to-moderate IR exposure.

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