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Preclinical model of radiation induced-neurotoxicity: longitudinal and multiparametric evaluation of tissue injury and cognitive deficits in the rat

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"Authors:

Elodie A. Pérès1, Gwenn Ropars1, Fatima-Azzahra Dwiri1, Carole Brunaud1, Jérôme Toutain1, Laurent Chatre1, Mikael Naveau2, Edwige Petit1, Myriam Bernaudin1, Samuel Valable1, Omar Touzani1

Affiliations:

1 Université de Caen Normandie, CNRS, Normandie Université, ISTCT UMR6030, GIP CYCERON, F-14000 Caen, France
2 Université de Caen Normandie, UNICAEN-CNRS-INSERM-CEA UAR3408/US50 Cyceron, GIP CYCERON, F-14000 Caen, France

Email address presenting author: peres@cyceron.fr

ABSTRACT

Introduction: Cranial radiotherapy (RT) has side effects, especially fatigue and cognitive deficits, which alter the quality of life of long-survivors. To improve the management of brain tumor patients treated by RT, it is crucial to propose sensitive tools to accurately detect radiation-induced brain injury. Based on a whole-brain irradiation (WBI) model in the rat, the aim of this study was to define magnetic resonance imaging (MRI) and blood biomarkers to predict brain damage underlying cognitive decline.

Materials and Methods: WBI (3x10 Gy) was performed on adult rats with a preclinical irradiator (X-RAD 225Cx). A longitudinal study was conducted in acute (1-2 weeks), early (1-3 months) and late (6 months) phases after WBI with complementary approaches. A battery of behavioral tests was done to quantify fatigue (homemade test/open field) and cognitive impairments (object recognition test/passive avoidance task). In parallel, sequential MRI analyses (7T Bruker) were undertaken to quantify brain volumetry, brain vascularization with cerebral blood volume (CBV) measurement as well as white matter integrity from diffusion tensor imaging (DTI). Immunohistochemistry (IHC) was performed to analyze blood vessels, astrocytes, microglia and white matter fibers. Blood markers of oxidative stress were also investigated: reactive species, 8-hydroxydeoxyguanosine (8-OHdG) and albumin.

Results: We reported a significant animal fatigue and a locomotor activity reduction from the first weeks until up 6 months. Short-term memory deficits were early evidenced whereas long-term memory is altered several months after WBI. Concerning MRI study, in the chronic phase, irradiated rats displayed a significant brain atrophy and reduced CBV. Interestingly, the analysis of mean diffusivity parameter based on DTI revealed significant early brain tissue modifications. Lastly, plasma levels of oxygen and sulfur reactive species as well as 8-OHdG raised in irradiated rats.

Conclusion: In this animal model of cerebral radiotoxicity, we highlighted that multiparametric MRI oxidative stress markers in plasma are relevant to detect early and late radiation-induced brain injury."

Orateur: PÉRÈS, Elodie (Unité ISTCT - UMR6030)

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