Review Article

INR INTERVENTIONAL NEURORADIOLOGY

Interventional Neuroradiology
0(00) 1–3

DOI: 10.1177/1591019916662380
ine.sagepub.com

SAGE

Should future interventional neuroradiologists be screened for mutations that impair radiation-induced DNA repair?

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Abstract

In our current medical practice, an increasing number of specialists now have access to radiology technical platforms in order to perform imaging-guided procedures. Although knowledge about the current guidelines and radiation protection devices is a pre-requisite for the use of radiation, the preventive measures are often more or less strictly followed, leading to chronic daily exposure to significant doses of radiation and large accumulated lifetime exposures. Aortic intervention, electrophysiology, and neuro intervention in particular can result in large doses to the operators. Interventionalists might try to rationalize their dismissal of the exposure risks with various excuses: they don't know where they left their badges (even though, guiltily, they would readily admit it is good practice to always wear them), the estimated short duration of the procedure, significant muscular strain and spasm caused by the heaviness of lead aprons, decreased dexterity with lead gloves, or discomfort in wearing lead protective glasses. But their dismissive attitude is most likely due to the inherent inability to feel threatened by something they cannot see or feel, a commitment to the patient at all cost, and a culture of bravado that reinforces their behavior.

Keywords

Radiation injury, cancer risk, genetic screening

Received 8 July 2016; accepted 12 July 2016

Introduction

In the last few years, prominent interventionalists have published their personal stories on the deleterious impacts of chronic radiation exposure on their health. In a documentary produced by the Organization for Occupational Radiation Safety in Interventional Fluoroscopy, Dr Ted Diethrich MD, world-renowned cardiovascular surgeon, revealed he had previously felt invincible to the effects of radiation, before being diagnosed with bilateral radiation-induced cataracts, premature left carotid artery atherosclerosis and a left brain oligodendroglioma.[1] Dr Lindsay Machan MD, interventional radiologist, and inventor of the drug eluting coronary stent, has for years warned his colleagues that there is no safe level of radiation exposure and the need to fully protect oneself against it, having himself suffered from bilateral radiation-induced cataracts.[2]

There is new evidence of the increased risk of radiation-induced cataracts even at low doses of radiation. The International Commission on Radiological Protection (ICRP) changed its eye lens dose thresholds in 2011, to a lifetime limit of 0.5 Gy and a yearly limit of 20 mSv/yr limit, with no year to surpass 50 mSv.[3] These new guidelines are much stricter than the previous 2007 guidelines allowing 150 mSv/yr eye lens dose.[4] This is a 1/7 of the previous average annual level.

Moreover, new data suggest that there might be a causal relationship between chronic exposure to radiation and the development of radiation-induced tumours. A recent case study documented 31 individual cases of interventionists diagnosed with various brain and neck tumors, showing 17 professionals affected with glioblastoma multiforme, five with meningiomas, and two with astrocytomas.[5] These three types of primary tumors are well known for their potential to be radiation-induced. Furthermore, a striking finding in this report was that there was 85% left-sided predominance of the lesions, hypothesized to be secondary to the X-ray beam being on the patients left during

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the procedures. Vitor Pereira MD has shown that the radiation dose to the left side of the head is 17 times higher than the right.

The mutation of a gene or multiple genes within a cell is the root and inception of all cancers. This change in the genetic sequence, if not corrected, can result in the production of proteins with abnormal or missing amino acid sequences, drastically effecting protein function. Indeed, in some cases it can result in no protein being produced at all. Genetic mutations can be categorized into two basic groups: acquired and germ line. Acquired mutations are the most common cause of cancer and arise from damage to DNA in somatic cells "acquired" during a person's life. They cause sporadic cancer and are not heritable, as the mutations are found in a group(s) of somatic cells only. Less common germ-line mutations are heritable, and arise from mutations in reproductive cells. This can result in the potentially cancer-inducing mutations being found in every cell throughout the body, including the reproductive cells of the ensuing progeny.

The integrity of our DNA is constantly under attack from products of cellular metabolism, viral infections, UV radiation, chemical exposure, and replication errors, all frequently causing genetic mutations. Naturally, there exists a plethora of cellular DNA damage repair mechanisms to rectify these mutations. However, it is the failure by these systems to recognize or repair DNA damage, or to trigger apoptosis, that results in the acquisition of mutations which can lead to cancer and other genetic disease. A single mutation is, therefore, unlikely to lead to cancer. Generally, it takes multiple mutations acquired over a lifetime to generate cancer. Ionizing radiation is a well-established mutagen, inducing mutation through a variety of molecular mechanisms including double-stranded DNA breaks, single-stranded DNA breaks, nucleotide substitution, and sugar ribose alterations.[6,7]

Many of the genes that aid in the propagation and advancement of cancer can be categorized into three broad groups: tumor-suppressor genes, oncogenes, and DNA-repair genes. Tumor suppressor genes generally limit cell growth by modulating cell mitosis, repairing certain kinds of DNA mismatch, or by inducing apoptosis if necessary. Tumor-suppressor mutations are normally loss of function, allowing cells to grow and divide at an unchecked rate, eventually forming a tumor. Oncogenes are any genes that when mutated or expressed at suitably high levels contribute to the transformation of a normal cell into a cancer cell. These types of mutations are not heritable, and are normally gain-of-function. Finally, DNA-repair genes fix mistakes and repair replication errors prior to cell division. Mutations of repair genes lead to repair failure and subsequent accumulation of potentially cancer-causing mutations.

There is extensive peer-reviewed literature focused on the effect of solar and galactic radiation on the health of airline crew members published by the Federal Aviation Authority (FAA). Airline crews have an occupational limit of 20 mSv/yr, and routinely accumulate between 3 and 7 mSv/yr.[8] However, when compared to ground crew and the normal population, their risk of cancer is still elevated by between 1 in 130 and 1 in 4800 for specific tumor types, depending on the number of block hours worked and the altitudes reached on the airline routes taken. Block hours are the time between the removal of the wheel chock from the airplanes tires prior to take off and the placement of a chock at the airplane tire at the destination airport. Trans Polar routes have particularly high radiation levels and flight crews are only allowed to perform a limited number of these flights per year. The higher the altitude the greater the radiation they receive. The relationship between flight distance and altitude is a well-associated risk of chromosomal translocations that could manifest into cancer.[9] In comparison, Canadian radiation workers are exposed to a cumulative dose of 6.3 mSv/yr,[10] and thus incur a significant level of risk of developing mutations that can contribute to cancer. A small percentage of Danish radiation workers managed to exceed 50 mSv/yr,[11] again increasing the risk of developing cancerous mutations. Interventionalists, Nurses and Technologists routinely exceed these radiation levels.

A competent DNA damage repair mechanism is essential to prevent radiation-induced mutation propagation. A healthcare professional with an inherited impairment of repair mechanisms will potentially be at increased risk of cancer induction by radiation-induced mutation. One strategy that could reduce the amount of potential risk to Interventionalists, Nurses and Technicians is the introduction of a pre-screening procedure for genetic predisposition to cancers caused by genetic mutations that arise as a result of exposure to ionizing radiation. In breast cancer and colorectal cancer screening for specific mutations in certain genes, or specific alleles of certain genes, to find out if someone is genetically predisposed is a well-established practice. Some populations have elevated risks. A classic example are Ashkenazi Jews who have a 1:50 chance of having a BRCA mutation which affects their ability to repair radiation induced DNA damage. Genetic screening could be performed before a graduate enters their residency or fellowship, with an aim to providing greater information about the risk that would be incurred by pursuing a medical career with radiation exposure. Most importantly a review of family history should be performed to detect a candidate with a family history of cancer. If genetic screening was to be performed this is now very cost effective. Genes to be sequenced for germ-line mutations would include BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, APC, MYH, TP53, PTEN, CDKN2A, and RET, but this is by no means an exhaustive list.

Humans are delicate organisms. We operate between a pH of 7.4 to 7.6, an HCT of 36–40, and a p02 of 93%–98%. Our DNA is not designed to tolerate

chronic daily radiation at the doses we now receive. As radiologists, it is our collective responsibility to ensure radiation protection awareness and promote a stricter application of the existing guidelines. More effective radiation protection is needed. The vast increase in demand for interventional services has increased our daily exposure. Our institutions and healthcare systems need to acknowledge our inherent risk of working with radiation and we should act as our own regulators so that every professional can safely practice without compromising their health, as there is no safe dose of radiation and a fundamental cultural shift is needed.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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