

Endocrine effects of Fukushima: Radiation-induced endocrinopathy

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ABSTRACT

The unfortunate accidents of Chernobyl and Fukushima have led to an enormous amount of radioactive material being released into the atmosphere. Radiation exposure to the human body may be as a result of accidents, such as those in Chernobyl and Fukushima, or due to occupational hazards, such as in the employees of nuclear plants, or due to therapeutic or diagnostic procedures. These different sources of radiations may affect the human body as a whole or may cause localized damage to a certain area of the body, depending upon the extent and dosage of the irradiation. More or less every organ is affected by radiation exposure. Some require a higher dose to be affected while others may be affected at a lower dose. All the endocrine glands are susceptible to damage by radiation exposure; however, pituitary, thyroid and gonads are most likely to be affected. In addition to the endocrine effects, the rates of birth defects and carcinomas may also be increased in the population exposed to excessive radiation.

Key words: Chernobyl, Fukushima, nuclear accidents, radiation exposure, radiation-induced endocrinopathy

INTRODUCTION

A devastating tsunami, caused by a violent earthquake of 8.9-Richter magnitude, struck the coastal areas of Japan on March 11, 2011. It caused extensive damage to life, property and infrastructure in the affected areas. The earthquake also damaged a nuclear installation located in Fukushima, leading to increased pressure and radiation levels in the reactor. Even after concerted efforts by the Japanese authorities, a large amount of radiation and radioactive material was released into the environment. The release of this radioactive material into the environment has created genuine concern among the medical community.

This unfortunate incident in Japan has brought back

memories of a similar nuclear accident which occurred on April 26, 1986, in Chernobyl. A very large amount of radioactive iodine-131 (I^{131}) and lesser amounts of short-lived iodine isotopes (iodine-129 and iodine-132 through iodine-135) were released intermittently over a period of 10 days after the accident. A large population was exposed to ionizing radiation, mostly from ingestion of radioiodine-contaminated food (particularly milk in children) and/or inhalation of radioactive isotopes dispersed in the environment.^[1] This immense radiation exposure affected not only Ukraine, but also many neighboring countries. The effects of the unfortunate incident are still being seen in the affected areas.

Similar effects are expected to be seen after the radiation exposure in Fukushima. Even though the level of radiation exposure in Fukushima does not match that of Chernobyl, it should be remembered that the situation in Fukushima is potentially worse since a major metropolis of 30 million people is close by.

This time, however, the medical community needs to be better prepared to handle the consequences of such a huge radiation exposure to a large population.

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EFFECTS OF THE RADIATION EXPOSURE IN CHERNOBYL

A few years after the nuclear accident in Chernobyl, a significant increase in the incidence of childhood thyroid carcinomas and autoimmune thyroid disease was observed. This was found to be associated with the excessive radiation exposure.^[2,3] People living in Chernobyl and adjacent affected areas were seen to have 50% lower sympathetic activity, 36% lower adrenal cortical activity and significantly lower blood cortisol levels. They also exhibited increased hypophyseal-thyroid system dysfunction, higher incidence of goiter and thyroiditis. An increased rate of secretion of gonadotropic hormones and accelerated sexual development in females was noted. Higher rates of congenital diabetes were also seen. Higher concentrations of thyroxine-binding globulin, lower concentrations of free T₃, and increased risk of non-toxic single nodular and multinodular goiters have been reported.^[4] Higher levels of prolactin and renin, with lower progesterone levels,^[5] have been documented.

This has led to continuous, chronic morbidity, even though the initial radiation exposure has passed long since. Children with congenital anomalies still continue to be born in the affected areas. A large number of mental and physical anomalies were seen in the children born soon after the accident.^[6] Down's syndrome, neural tube defects, chromosomal abnormalities, cardiovascular diseases, immunologic disorders, lens changes, cancer, mental retardation, thyroid diseases and leukemias were some of the more frequent problems seen in the children from affected areas.^[7]

One hopes that such a situation will not be repeated in Japan.

PATHOPHYSIOLOGY OF RADIATION-INDUCED DAMAGE

The harmful effects of ionizing radiation, especially its carcinogenic potential, are fairly well known. Ionizing radiations above a threshold level, which varies for each organ, lead to tissue destruction. However, even at levels below the threshold level, damage can occur to functional and structural proteins in the cells, including DNA and RNA.

In addition to burns and radiation sickness which may themselves lead to immediate death, there are some delayed effects of a high-dose radiation exposure as well. The delayed effects cause most damage to the rapidly dividing

cells of the body and to those cells which have an inherent ability to concentrate the radioactive materials. An example of the latter includes the thyroid gland, which concentrates radioactive iodine. Due to the rapid cell division and growth in fetuses, they form a group more prone to be affected by radiation exposure. This is consistent with the morbidity pattern seen after Chernobyl.

OTHER TYPES OF RADIATION EXPOSURE

Ultraviolet radiation (UVR) whether of solar or artificial origin, is a known carcinogen. Excessive exposure to UVR increases the risk of several types of cancer, cortical cataract, some conjunctival neoplasms, ocular melanoma, autoimmune and viral diseases.^[8]

Iatrogenic radiation exposure, for diagnostic or therapeutic purposes, holds the same risks as does environmental radiation exposure. However, a key difference is that in most iatrogenic cases the radiation exposure is focused and concentrated on a specific region of the body. Although the radiation exposure involved in this case may be less, repeated exposure may lead to considerable tissue damage.

Although diagnostic imaging such as X-rays and computed tomography (CT) scans provide great benefits, their use is associated with small increases in cancer risk.^[9] Similarly, mammography, although very useful, is associated with the amount of radiation that an ordinary person would be exposed to over a 3-month period.

Exposure to diagnostic radiography *in utero* has been associated with increased risk of childhood cancer, particularly leukemia.^[10] Radiation is a well-known etiology for many central nervous system (CNS) tumors as well especially meningiomas, sarcomas and gliomas.^[11]

ENDOCRINE EFFECTS OF RADIATION EXPOSURE

Radiation exposure affects virtually every endocrine gland, but to different degrees. While some glands such as pituitary, thyroid and gonads are sensitive to radiation, the adrenal is extremely resistant.

Pituitary

The risk of developing pituitary tumors after exposure to ionizing radiation is increased. Even small doses (i.e. <1 Sv) are associated with statistically significant higher risks for CNS and pituitary gland.^[12] A study conducted on the nuclear bomb survivors of Hiroshima and Nagasaki showed that the excess relative risk per sievert (ERR_{Sv}) of pituitary gland tumors was $ERR_{Sv} = 1.0$ (95% CI =

0.2 to 3.5).^[12] Although rare, pituitary adenomas after radiation therapy of the head and neck region have been reported.^[11] Patients treated with brain tumors frequently develop hypothalamic–pituitary dysfunction which may lead to growth hormone (GH) deficiency, hypothyroidism, gonadal or adrenal dysfunction.^[13] A gonadotropin-releasing hormone (GnRH) deficiency related decrease in serum luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone is seen in these patients.

In some of the patients presenting with deficiencies of anterior pituitary hormones, hypothalamic dysfunction is the cause.^[14] Although the deficiencies most commonly develop in the order GH, gonadotrophins, adrenocorticotrophic hormone (ACTH) followed by thyroid stimulating hormone (TSH), this sequence may not be predictable in an individual patient. Comprehensive testing is therefore indicated. Investigations should ideally be performed annually, for at least 10 years after treatment or until deficiency has been detected and treated.

It is not only the patients with pituitary disease who are at risk of developing hypopituitarism after radiotherapy, but also any patient who receives a total dose of irradiation of 20 Gy or more to the hypothalamic–pituitary axis is at risk of hypopituitarism, although the threshold dose may be lower than this.^[15] Cranial radiation at low doses is associated with accelerated puberty in exposed individuals; however, girls are affected more than the boys.^[16]

Thyroid and parathyroid

The endocrine gland most commonly affected by external radiation is the thyroid. The effect of exposure to leaked radioactive substances on the thyroid was first observed after Chernobyl. As previously discussed, the incidence of thyroid carcinomas and other thyroid diseases rose significantly after irradiation. Multiple hypotheses have been postulated to explain the radiation-induced carcinogenic processes in the thyroid gland. These include radioactive iodine being concentrated in this gland^[17] and impairment of the ability of T cells to fight cancerous cells.^[18]

Stable iodine supplements (such as potassium iodide) can be used prophylactically to decrease the risk of cancer development in the people exposed to radiation.^[19] However, the effectiveness of this method decreases significantly after 3 hours of radiation.

Thyroid and parathyroid diseases after head and neck irradiation are well known. Radiation doses to the thyroid that exceed approximately 26 Gy frequently produce hypothyroidism, which may be clinically overt or subclinical. Pituitary or hypothalamic hypothyroidism may arise when

the pituitary region receives doses exceeding 50 Gy with conventional 1.8–2 Gy fractionation. Direct irradiation of the thyroid may increase the risk of Graves' disease or euthyroid Graves' ophthalmopathy. Silent thyroiditis, cystic degeneration, benign adenoma, and thyroid cancer have been observed after therapeutically relevant doses of external radiation. Direct or incidental thyroid irradiation increases the risk for well-differentiated, papillary, and follicular thyroid cancer from 15- to 53-fold.^[20] Hyperparathyroidism has also been reported with the same frequency in the patients who have undergone radiation therapy in head and neck region.^[21]

Pancreas

Although literature associating pancreatic disease with radiation exposure is unavailable, studies have associated radon exposure to pancreatic cancer.^[22] Radon, a radioactive gas produced by decay of uranium, has been shown to be a significant risk factor for pancreatic cancer by a number of studies. Thus, we may presume that excessive radiation exposure may lead to an increased risk of pancreatic disease; however, studies are needed to provide evidence for this.

Adrenals

The adrenal gland is quite resistant to radiation exposure. However, radiation exposure may affect the pituitary gland and lead to decreased secretion of ACTH. This is evidenced by the fact that the serum ACTH levels of Chernobyl accident survivors were below normal.^[5] In a large radiation exposure, the adrenal gland may be affected directly as well.^[5] This may lead to a decrease in adrenal function and a lower circulating level of cortisol and other adrenal gland hormones. Morphological disorders were seen in the adrenal gland, thyroid gland and ovaries of the rodents inhabiting the area exposed to radiation in Chernobyl.^[23] Gene mutations and chromosomal abnormalities were also seen. This may suggest that similar changes could also have occurred in the adrenal glands of human survivors.

Gonads

Gonads are also profoundly affected by irradiation. Irradiation to the CNS may affect the timing of the onset of puberty, result in hyperprolactinemia, or cause gonadotropin deficiency if the hypothalamic–pituitary axis is involved in the radiation field. Abdominal, pelvis, spinal or testicular radiotherapy may directly affect the gonads and lead to less sex steroid production and infertility. If this happens in a child, pubertal development either may not occur or may be arrested.

Ionizing radiation has been shown to be a significant risk factor for spontaneous abortions if exposure occurs

during pregnancy. It can also lead to infertility in men and women.^[24] Direct irradiation may affect the uterus, which may cause arrested growth in prepubertal girls and miscarriages in pregnant women; the ovaries, which may drastically decrease the number of oocytes which may lead to infertility and may even induce menopause if the patient is above 40 or the dose used is very high; or the testes, which causes aspermia. The aspermia may be temporary or permanent, depending on the dose of radiation and its timing.^[25]

The effects of radiation therapy on the reproductive system are especially significant because patients may want to cryopreserve their eggs or sperms for later use. The severity of these effects can be seen by the fact that 1 in every 6 women exposed to radiation therapy in childhood experienced ovarian failure.^[26]

Childhood total abdominal radiation therapy in girls has been shown to cause marked inhibition of follicular growth and decreased oocyte number. They had elevated FSH and low estradiol number and failed to undergo complete pubertal changes. The average menopausal age was also reduced.^[25] However, flank irradiation decreased the risks of development of these complications as compared to total abdominal irradiation.

In women who have undergone total abdominal irradiation during childhood, the chances of carrying a pregnancy to term are decreased.^[27] Although ovarian failure could be implicated in some of these cases, most of them were due to developmental defects in the uterus. The radiation led to a smaller uterine length and decreased blood supply of the uterus.^[28] The endometrium was seen to be unresponsive to exogenously supplied progesterone and estradiol. This shows that radiation to the abdomen may have severe consequences and may lead to infertility later in life, even if ovarian function is preserved.

The effects of radiation, whether therapeutic or accidental, on the testes are dose dependent. Radiations damage the Leydig or Sertoli cells after which no proliferation takes place. It also damages the spermatogonia, spermatocytes and spermatids. Spermatogonia are the most prone to damage by radiations, followed by spermatocytes and then spermatids. Spermatids usually show no damage at low doses of radiation. This is why sperm levels may be normal up to 40–50 days after the radiation exposure. However, after this time period, the number of spermatogonia dividing to form new cells is diminished, thus leading to temporary or permanent oligo- or aspermia. Depending upon the dose to which the testis was exposed, spermatogonia A may start division after a lapse of a few months to years.^[25]

CONCLUSION

Radiation exposure has profound effects on the endocrine system. Unfortunate incidences as the ones in Chernobyl and Fukushima leave long-lasting scars on the human health. The general recommendation in this situation is to examine the survivors of radiation exposure annually for at least 10 years after the last exposure.

However, in our modern world, where nuclear plants and radiation energy have become quite common, it is imperative that all doctors be prepared to handle the potential adverse effects that these may lead to. For this, there is a need to teach the management of radiation-related medical problems from the undergraduate medical curriculum onward. Radiation-related endocrinopathy should be highlighted and discussed by endocrinologists at every possible forum.

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