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Nikolai Hristov*

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Review Article

Radiation-induced eye impairments

V. Zahariev [1], N. Hristov [2]*, St. Vizev [1], P. Angelova [1]

[1]Department of Preventive Medicine, Medical University-Sofia.

[2]Department of Social Medicine, Medical University-Sofia.

***Corresponding Author:** Nikolai Hristov, Department of Preventive Medicine, Medical University-Sofia.

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Abstract:

The problem of the impact of ionizing radiation on eye structures is one of the most important and topical in radiobiology. Knowledge of tissue radiosensitivity and induced tissue changes in the eye is essential for understanding the nature of radiation damage and the behavior of medical professionals. In this publication, the early and late determined radiation-induced impairments of the eye are presented as a result of radiotherapy or radiation incidents. The risk factors determining post-irradiation eye reactions, pathophysiological mechanisms, clinical picture, diagnosis, prevention, and new approaches in therapy are presented. We found that the typically found radiation-induced eye impairments are those of the eyelids – dermatosis and madarosis, conjunctiva – acute conjunctivitis, varied damage to the lacrimal apparatus, cornea – edema and ulceration, iris – rarely inflammation or neovascularization, sclera – rarely atrophy or necrosis, eye lens – cataract, retina – characteristic retinopathy, and optical nerve – rarely neuropathy. We provide the current consensus on prevention and treatment protocols in radiation-induced eye impairments, though most suggested treatment so far should qualify as experimental.

Key words: ionizing radiation; radiation-induced eye impairment; radiotherapy; radiation incidents; post-irradiation eye reactions

Introduction

The aim of our study was to summarize and describe the current scientific consensus on the possible radiation-induced eye impairments, circumstances under which they arise, and identify the available prevention and treatment options. To this end, we performed a systematic literature review in 2023. Keywords entered in relevant databases such as PubMed, were ionizing radiation, radiation-induced eye impairment, radiotherapy, radiation incidents, post-irradiation eye reactions. Languages used during the literature search were English, German, French and Russian, though we settled finally on citing English and German sources.

The effects of ionizing radiation on the eye were first described by Chalupecky as early as 1897 [1]. In-depth systematic studies on the action of ionizing radiation on the structures of the eye began to be conducted by Rohrschneider, who in 1929 proposed a scale reflecting the different radiosensitivity of the eye structures - starting with the lens, as the most radiosensitive tissue, followed by the conjunctiva, the cornea, the uvea, the retina and ends with the most radiation- resistant – the sclera [2]. Poppe continued these studies and in 1942 published their results [3]. The first scientific reports describing the effects of ionizing radiation on the eyes of those working in such an environment - with a cyclic accelerator (cyclotron) were made by Abelson and Kruger, and in individuals who survived the atomic bombings, by Cogan et al. in 1949. Early damage mainly affects the rapidly proliferating epithelial cells and occurs during the course of irradiation or several weeks after. Blepharitis, conjunctivitis and keratitis usually develop. Late radiation-induced damages develop after a latent period of several months to tens of years, depending on the individual biological characteristics and the absorbed dose. These changes are mainly due to endothelial damage and microcirculatory dysfunction or to genomic damage to epithelial cells that do not die immediately after irradiation but have the potential to divide and differentiate, as in radiation cataract. Typical late radiation-induced injuries are cataracts, radiation retinopathy, and radiation-induced optic neuropathy [4, 5].

Eyelids

Early radiation-induced damage to the eyelids includes dermatitis and madarosis at cumulative doses > 20 Gy with conventional fractionation, and extremely rarely at doses of 10 Gy delivered over three days. Loss of eyelashes can cause irritation conjunctiva and cornea. The skin of the eyelids reacts to ionizing radiation like the skin of other anatomical sites. The first reaction is erythema (usually after 2 weeks), which is followed shortly by dry desquamation. The skin at this time is warm and sometimes edematous. Microscopically, the overlying dermal vessels are dilated and an inflammatory infiltration with granulocytes, macrophages, eosinophils, plasma cells, and lymphocytes is observed. Erythema is

usually transient and resolves quickly [6]. Hamilton et al. found that predisposing factors for increased skin radiosensitivity were advanced age, previous prolonged sun exposure and male gender. At cumulative doses exceeding 50 Gy, moist desquamation, sometimes secondary infection, and cicatrixes, resulting from unhealed ulcers, more often develop.

Late radiation-induced damage to the eyelids is relatively rare. These include telangiectasia and skin atrophy, permanent loss of eyelashes and depigmentation, usually at cumulative doses > 50 Gy. Fibrosis, scarring, and clinically significant eyelid deformity may develop. Regrowth of eyelashes sometimes leads to trichiasis or distichiasis, intense pain caused by growing eyelashes, irritation and even ulceration of the cornea. Keratinization of the palpebral conjunctiva, especially of the upper eyelid, may also cause corneal damage. Cicatrization can lead to entropion or ectropion [6].

Conjunctiva

Acute radiation-induced conjunctivitis occurs relatively frequently at doses ≥ 30 Gy. Studies by Stafford et al. found manifestations of radiation conjunctivitis in 46% of patients treated for orbital lymphoma with a mean cumulative dose of 27 Gy [7]. Clinical symptoms are characterized by conjunctival injection, often accompanied by significant chemosis, watery discharge and discomfort. Secondary bacterial or less commonly viral infections, usually from adenoviruses, may develop. Patients have the feeling of sand in the eye and piercing pain. There may be rhinorrhea or other respiratory symptoms. Viral conjunctivitis is often accompanied by enlarged periauricular lymph nodes, which helps in the correct diagnosis. Late radiation-induced damage to the conjunctiva usually occurs at doses ≥ 35 Gy. Conjunctival telangiectasias are relatively common. Stafford et al. described such vascular changes in the conjunctiva, in patients treated for orbital lymphoma, even at doses of 30 Gy [7]. Subconjunctival hemorrhages develop rarely and do not threaten vision. Chronic conjunctivitis, squamous epithelial metaplasia, and conjunctival keratinization have been observed at doses exceeding 50 Gy. In parallel, corneal abrasion may also occur. At doses > 60 Gy, permanent damage to the conjunctiva can cause symblepharon, leading to desiccation or restriction of eye movements [7].

Lacrimal apparatus

Early radiation-induced xerophthalmia results from either damage to the acinar cells of the lacrimal gland or damage to the meibomian glands, which are the major source of tear lipids and maintain normal tear film stability. Dysfunction of the Meibomian glands in itself is a state of inflammation and contributes to disruption of homeostatic regulation of the tear film and development of dry eye syndrome (DES, keratoconjunctivitis sicca). The pathology of the "dry eye" syndrome is more accurately represented by the term "ocular surface disease". It is categorized into three degrees – mild, moderate and severe, with the severity of the clinical symptoms being directly dependent on the dose and varying from itching, burning, feeling of a foreign body and fatigue in the eyes to severe redness, inflammation and pain. Various methods are used to diagnose and assess the severity of the disease – biomicroscopy; examination of the basal tear production by means of the Schirmer test; diagnostic staining of the anterior eye segment with fluorescein, rose bengal, lissamine green; measuring the osmolality of the tear film; determining the size of the tear meniscus; study the stability of the tear film, by tracking the time to tear; meibography, etc., through the use of corneal topographers. The standardized questionnaire OSDI (Ocular surface disease index) can be used to objectify the severity of the subjective symptoms and the effectiveness of the therapy. Early effects include conjunctival inflammation, chemosis, and tear film instability with subsequent dry eye sensation. These symptoms usually subside, but sometimes they can be quite persistent [8]. Kennerdell et al. reported that at doses of about 25 Gy for the treatment of orbital lymphoma, half of the patients had an early mild form of xerophthalmia. With moderate dose irradiation, between 30 and 45 Gy, late manifestations of dry eye syndrome manifest after 4 to 11 years. High doses of ionizing radiation aggravate the clinical picture and lead to a permanent decrease in the number of Goblet cells and loss of serous acinar cells. According to Merriam et al. the risk of atrophy and fibrosis of the lacrimal gland increases significantly with cumulative doses ≥ 50 Gy conventional fractionation, as well as after a single dose of 20 Gy. At doses above 57 Gy, severe dry eye syndrome develops [9]. Clinical symptoms appear within 1 month after irradiation, with dry eye usually resulting in vascularization and corneal opacification, which appear after 9 to 10 months. Doses > 60 Gy result in permanent loss of lacrimal secretion and profound keratoconjunctivitis sicca. Patients with severe lacrimal gland dysfunction complain of burning, redness, thick secretion, "foreign body sensation", blurred vision and photophobia. Dry eye syndrome can progress to vision loss, corneal opacification, ulceration, and vascularization. In rare cases, complications of secondary infection or perforation may occur. Bulbar phthisis and symblepharon can sometimes be seen. The tolerated doses to the lacrimal gland with conventional fractionation are similar to the tolerated doses to the salivary glands and are estimated to be about 30 to 40 Gy [9]. According to Emami et al., TD 5/5 (5% risk of dry eye syndrome over 5 years) was estimated at 35 Gy and TD 50/5 (50% risk of dry eye syndrome over 5 years) at 50 Gy [10] Studies by Parsons et al. showed a negligible risk at doses < 30 Gy, a sharply increasing risk at doses > 40 Gy, and 100% development of severe dry eye syndrome at doses > 57 Gy [11, 12]. Doses ≥ 60 Gy often cause stenosis of puncta lacrimalia, canaliculi lacrimales, or ductus nasolacrimalis. Radiation-induced canaliculitis can lead to fibrosis and canalicular obstruction. McCartney et al. found that concomitant systemic chemotherapy with paclitaxel significantly increased the risk of stenosis [13].

Cornea

Early radiation-induced damage to the cornea is mainly due to tear film dysfunction and the development of secondary dry keratitis. In addition, ionizing radiation can directly damage the epithelial surface, stroma, and endothelium of the cornea. Barabino et al. found that punctate epithelial erosions were common after doses of 30 to 50 Gy of conventional fractionation [14]. Patients with keratitis have a characteristic triad of symptoms (frequent blinking, lacrimation and photophobia). Epithelial erosions usually resolve within a few weeks or months after radiation. Very rarely they can last months or years. Corneal edema has been observed after total doses of 40 to 50 Gy, resulting from loss of the intact corneal epithelial barrier or endothelial dysfunction. Swelling may be transient or persist indefinitely. Depending on the timing, size, and location of the swelling relative to the visual axis, patients may be asymptomatic or complain of photophobia, "foreign body sensation," burning, pain, blurred, or decreased vision [14]. According to Barabino et al., corneal ulceration may occur due to destruction of the corneal epithelium or stroma, at cumulative doses > 60 Gy fractionated irradiation or 20 Gy single dose. Ulcerations usually cause pain, redness, discharge, tearing, photophobia, and decreased vision. The combination of xerophthalmia and corneal ulceration can lead to irreversible vision loss due to scarring and perforation. Doses above 50 Gy, although rare, can cause radiation-induced corneal decompensation months after radiation therapy, possibly as a result of stem cell loss. Smith et al. reported isolated cases with persistent corneal conjunctivitis (a condition in which the cornea is covered by an unstable, opaque conjunctival epithelium, often with secondary neovascularization and stromal scarring) several years after radiotherapy [15]. There is little information in the scientific literature regarding tolerable corneal doses for conventional fractionated irradiation. TD 5/5 is estimated at 30 Gy and TD 50/5 at 50 Gy.

Iris

The iris is relatively radioresistant and acute radiation-induced damage is rarely reported. Early transient iritis may develop after single doses of ≥ 10 Gy. Severe persistent anterior uveitis has been observed with cumulative doses of 30 to 40 Gy hypofractionation (10 Gy fraction) and after 70 to 80 Gy conventional fractionation (over 6–8 weeks) [16]. Clinical symptoms are characterized by pain localized or radiating to the eyebrow and temple, photophobia, red eyes, and blurred vision. Recurrent manifestations of severe iridocyclitis, with fibrin exudate, deposition of precipitates on the posterior endothelial surface of the cornea, and formation of posterior synechiae between the pupillary margin of the iris and the anterior surface of the lens may be observed. Direct damage to iris vessels and resulting ischemia can cause local proliferation of iris vessels. It has also been suggested that the release of humoral factors from irradiated tumor tissue may stimulate neovascularization in the iris (iris rubeosis). The growth of neo vessels in the anterior chamber angle leads to disruption of the outflow of the intraocular fluid and to the development of neovascular glaucoma [16]. Neovascular glaucoma was first described in 1871, and in 1906 Coats described the formation of neo vessels in the iris in individuals with central retinal vein occlusion [17]. Weiss et al., introduced the term neovascular glaucoma in 1963. It is now clear that a number of ocular and systemic diseases in which retinal ischemia and/or hypoxia occur with subsequent release of angiogenic factors lead to neovascular glaucoma. Radiation-induced neovascular glaucoma is a late complication that develops in up to 20% of cases after radiotherapy in the eye area. Iris neovascularization and neovascular glaucoma are almost always ischemic. Risk factors include high doses of ionizing radiation, diabetes mellitus, vitreous hemorrhage, and retinal detachment. Symptoms include eye pain, headache, photophobia, reduced vision, and redness. Localized iris atrophy has been observed after radiotherapy of iridociliary melanomas but not after therapy of orbital tumors [18].

Sclera

The sclera is predominantly avascular and is the most radioresistant ocular tissue. Radiation- induced scleral damage includes loss of episcleral vessels, scleral thinning, and perforation. A number of authors, such as Tarr & Constable, Petrovich, Hirst, Shields et al., have reported atrophy and necrosis of the sclera after radiotherapy, mainly brachytherapy [19, 20, 21, 22, 23]. These impairments are serious dose-limiting factors in episcleral brachytherapy. Scleral atrophy is of particular importance in adjuvant brachytherapy after surgical excision of the pterygium. Predisposing factors are surgical intervention, damaged conjunctiva and dry eye syndrome. Studies by MacKenzie et al. found 13% scleral atrophy after brachytherapy (99 cases of 747 treatments performed, 95% of which received 22 Gy and 5% 18 Gy in single fractions) with a follow-up of more than 10 years. Scleral atrophy can be complicated by bacterial or fungal infection, with the development of corneoscleritis and endophthalmitis. A long latent period, ≥ 20 years, as well as some diseases such as posterior scleritis, serous retinal detachment or orbital pseudotumor (idiopathic orbital inflammation, orbital inflammatory syndrome) may mask scleral atrophy and make diagnosis difficult [24].

Eye lens

The eye lens has the highest degree of radiosensitivity compared to other eye tissues. It is also one of the most radiosensitive tissues in the human body. In 1908, Birch-Hirschfeld identified the first case of radiation-induced cataract [25]. The action of ionizing radiation on the eye leads to characteristic changes in the lens, including the development of cataracts. In the initial stage, there is clouding, usually without visual disturbances, but the severity of these changes can progress, depending on the ingested dose and the time after exposure, and require surgical intervention. There is an inverse relationship between dose load and latency period. Recent data from animal models and irradiated human populations strongly suggest that lens opacification occurs even at doses much lower than those generally considered to be cataractogenic, and these observations are consistent with a small or even nonexistent threshold. of the dose. Changes in the lens are noted in the dose range 0.2 – 0.5 Gy, while ocular pathology in other tissues develops with acute or fractionated irradiation in the dose range 5 – 20 Gy. Published results from chronically exposed workers suggest a long-term risk for cataracts and the need for eye protection even at low doses. Based on currently available data, it can be concluded that the threshold dose for radiation-induced cataract is approximately 0.5 Gy, regardless of the nature of irradiation (acute, chronic, or fractionated) [26]. In addition to reducing the threshold, the ICRP also proposed a drastic reduction in the annual limit of equivalent dose to the eye lens for personnel working with sources of ionizing radiation, from the current 150 mSv to 20 mSv [26]. Some authors even support the hypothesis that radiation-induced cataract is a stochastic process [27]. In this regard, the United Nations Scientific Committee on the Study of the Effects of Atomic Radiation (UNSCEAR) concluded that there are effects which, at this stage, cannot be classified as either deterministic or stochastic [28]. Until recently, it was believed that ionizing radiation mainly causes posterior subcapsular cataract (PSC), characterized by rapid progression. A number of large-scale radio-epidemiological studies covering atomic bombings survivors, Chernobyl liquidators, astronauts, etc., have shown that ionizing radiation can also induce cortical cataract (CC) and nuclear cataract (NC) [29, 30]. Clinical and histological changes in the eye lens during radiation cataractogenesis are characteristic of all vertebrates and proceed identically. Early signs usually include opacification beginning along the visual axis, often in the posterior subcapsular region of the lens. A custom-designed, modified Merriam-Focht method was used to quantify the earliest radiation-induced changes in the lens. The method is based on the fact that radiation cataract develops consistently and progressively. Slit-lamp biomicroscopy allows the identification of at least four easily recognizable stages that form the basis for quantitative assessment of cataract severity. This method was used by Worgul et al., to study the Chernobyl liquidators [31]. A generally accepted method for the quantitative analysis of cataracts with different etiology is the LOCS (lens opacification classification system), with several versions. Version III of the LOCS was used by Minamoto, Nakashima et al., in studies of atomic bombing survivors [32, 33]. The exact mechanisms of radiation cataract formation are not known. According to Hanna, O'Brien, Worgul, Rothstein, Jose, Kleiman, Blakely, Holsclaw, and many other researchers, ionizing radiation exerts a cataractogenic effect on the lens epithelium by damaging the genome, leading to mutations and/or disrepair of epithelial cells, which do not die immediately after irradiation [34, 35, 36, 37, 38, 39, 40, 41]. Genomic damage resulting in altered cell division, transcription and/or abnormal differentiation of fibrillar lens cells is considered the most significant. Radiation cataract formation primarily depends on the survival and potential division and/or differentiation of lens epithelial cells with compromised genomes. Abnormally dividing and/or differentiated epithelial cells in the pre- equatorial zone of the lens are thought to migrate predominantly to the posterior pole, where they form opaque lens fibers. Ionizing radiation-induced defects in cell signaling, various growth factors, including fibroblast growth factor (FGF) and cyclin-dependent kinases (CDKs), production of extracellular matrix proteins, as well as cell death and apoptosis, may play an important role in determining the future abnormal epithelial cell division, differentiation and migration. Matsuda, Worgul, Babizhayev, Spector, Hamada, Uwineza and others identified oxidative stress as a major initiating event in the development of radiation-induced cataract. Experimental cell culture setups show that such stress leads to metabolic and cellular changes similar to those seen in human cataracts. Changes in cellular reduction potential, membrane function, mitochondrial viability, and DNA damage appear to be the earliest events following oxidative stress. It is likely that unrepaired DNA damage to the lens epithelium leads to cataract development. There are also some facts proving the link between DNA damage and cataractogenesis: an increased frequency of

micronuclei, a marker of genomic damage, in the epithelium of cataract patients; the increased frequency of single-stranded DNA breaks in the epithelium of cataract patients; association between low or high LPE ionizing radiation and PSC cataract development; association between bilateral cataracts and certain human genetic disorders involving defects in DNA repair mechanisms such as – Cockayne syndrome, PIBIDS syndrome (photosensitivity, ichthyosis, brittle hair, intellectual disability, reduced fertility and short stature), Werner syndrome and Rothmund-Thomson syndrome [42, 43, 44, 45, 46, 47, 48].

Retina

Radiation retinopathy is a chronically progressive microangiopathy and is a well-known radiation-induced injury. It was first described in 1933 by Stallard after radiotherapy for retinoblastoma [49]. In isolated cases it was observed even at doses below 15 Gy. Elsås et al. reported a case of bilateral radiation retinopathy in a 32-year-old man with an estimated dose of 11 Gy [50], but a dose in excess of 30 Gy is usually required to produce the typical changes [51]. According to Parsons et al. a higher risk of radiation retinopathy exists at doses greater than 45 Gy [52]. The time to onset of radiation retinopathy is usually between 6 months and 3 years, but sometimes longer. It is directly dependent on the size of the dose and the combination with chemotherapy. Patients with diabetes, hypertension, or previous chemotherapy are more susceptible to radiation-induced retinopathy [53, 54]. Pregnancy is thought to accelerate radiation retinopathy [55]. It occurs most often after radiation treatment of retinoblastoma, tumors of the paranasal cavities and nasopharynx. It is due to endothelial cell damage leading to chronic progressive vasculopathy of precapillary arterioles, retinal capillaries and postcapillary venules. Microvascular changes reduce perfusion and trophicity of retinal tissues. The most radiosensitive is the posterior polar region of the retina [56]. Patients usually have reduced visual acuity. Vision loss in patients with radiation retinopathy is usually progressive and irreversible due to impaired macular perfusion. Histologically, thickening of arteriolar and capillary walls and loss of endothelial cells were observed. These findings differ from diabetic retinopathy in that there is an early loss of endothelial cells, whereas pericytes are initially affected in diabetic retinopathy. Furthermore, radiation retinopathy usually has fewer microaneurysms than diabetic retinopathy [57]. From a clinical point of view, radiation retinopathy can be classified as non-proliferative and proliferative. In nonproliferative retinopathy, pathological changes are limited intraretinally. The proliferative form represents an angiogenic response of the retina to overcome ischemia resulting from extensive capillary occlusions. In this clinical form, pathological changes spread beyond the retinal surface. Radiation-induced retinopathy is diagnosed by ophthalmoscopy, fluorescein angiography, and optical coherence tomography (OCT). Clinical manifestations are similar to diabetic retinopathy and include microaneurysms, telangiectasias, increased vascular permeability, intraretinal and macular edema, retinal hemorrhages, hard exudates, cotton wool spots (signs of vascular insufficiency representing terminal axonal swellings, resulting from terminal retinal arteriolar occlusion) and capillary obstruction. The ischemic retina produces angioproliferative factors, ultimately leading to the neovascularization and vitreous hemorrhages that occur in proliferative retinopathy. Frequent hemorrhages and neovascularization can lead to tractional retinal detachment and neovascular glaucoma. In the late stages of neovascularization, fibrous tissue grows in an attempt to provide a supportive structure to the neo-vessels. Fibrosis increases the risk of tractional retinal detachment. The pathogenetic mechanism of the occurring changes is not fully understood. The endothelium lining the vessels is a major unit in the maintenance of hemostasis. It performs an anti- inflammatory, anti-thrombogenic and barrier function in terms of vascular permeability, while at the same time regulating vascular tone. Their activation or induction by various factors stimulates the expression of adhesion molecules [57]. The endothelium is a major target for the action of free inflammatory mediators' radicals and cytokines [58]. Reactive oxygen radicals (ROS) and oxidative stress are considered as potential stimulators of various inflammatory pathways that induce the overexpression of adhesion molecules and inflammatory cytokines. These adhesion molecules facilitate the attraction and accumulation of leukocytes, platelets, and possibly erythrocytes to the endothelium. Overproduction of ROS and lipid peroxides as a result of the action of ionizing radiation contributes to the development of endothelial and microcirculatory dysfunction [59, 60]. Studies with human retinal cells have established that ionizing radiation induces leukocyte adhesion

through mechanisms involving p38 mitogen-activated protein kinase (MAPK), p53, and ICAM-1 activation. MAP kinases play a key role in chronic inflammation. One of them, p38MAPK, is activated upon cellular stress and regulates the expression of inflammatory cytokines, chemokines and proteinases. Radiation-induced DNA double-strand breaks induce activation of p38MAPK through phosphorylation and accumulation of p53 in human endothelial cells. Activated p53 promotes the transcription of inflammatory and apoptotic genes, such as ICAM-1 [61, 62]. In support of this is the fact that inhibition of p38 MAPK results in a reduction of both inflammatory and proapoptotic signaling [61, 63, 64]. A number of studies have found that hypoxia up-regulates the expression of vascular endothelial growth factor (VEGF), under which the retinal pigment epithelium and retinal glial cells release this factor. VEGF is a major proangiogenic factor, also stimulating vascular permeability [65, 66]. VEGF-A plays a major role in angiogenesis. VEGF has been suggested to contribute to the pathogenesis of radiation-induced macular edema [67, 68, 69]. In addition, other factors and cytokines, including IL-1, IL-8, as well as ICAM-1, also contribute to vascular permeability and the pathogenesis of macular edema [70, 71, 72]. Inflammatory cells - leukocytes and macrophages also participate in the pathophysiology, causing occlusion and impaired capillary perfusion.

Optical nerve

Radiation-induced optic neuropathy is a rare, late complication first reported by Forrest et al. in 1956 (73). Then they define it as a sudden and profound, irreversible loss of vision, due to damage to the optic nerves or damage to the chiasm caused by radiation therapy. The latent period in humans varies from 3 months to 8 years, but is most commonly observed 18 months after exposure (74, 75, 76). Radiation-induced optic neuropathy is a form of delayed radionecrosis of the anterior peripheral part of the optic pathway (before the corpus geniculatum laterale i.e. n. opticus, chiasma opticum and tractus opticus). Vision loss can be unilateral or bilateral, simultaneous or consecutive. Cumulative doses exceeding 50 Gy are usually required for its development. According to Emami et al. the doses corresponding to a 5% and 50% probability of blindness within 5 years of radiotherapy are 50 and 65 Gy, respectively (10). QUANTEC (quantitative analysis of normal tissue effects in the clinic) doses are similar (77, 78, 79). Analysis of the results showed that age over 60, female gender and chemotherapy significantly increased the risk of radiation optic neuropathy, while diabetes and hypertension did not have as significant an effect as for radiation retinopathy. It can also develop as a consequence of radiation-induced retinopathy (80, 81, 82). The pathophysiological mechanisms are not yet fully understood. Radiation-induced optic neuropathy is most likely due to damage to the vascular endothelium, with the development of microvascular insufficiency, hypoxia and subsequent damage to the surrounding nerves, through the development of demyelination and reactive astrocytosis. Some data already exists on direct radiation damage to the visual pathway. Radiation optic neuropathy is usually characterized by rapid and irreversible, unilateral or bilateral, painless loss of vision within several weeks. A scale was developed for the clinical evaluation of radial optic neuropathy by examining vascular changes in the radial peripapillary capillary plexus (RPCP) using optical coherence tomography angiography (OCT-A) [76, 83, 84, 85, 86, 87, 88].

Prevention and treatment

For many years, various pharmacological compounds have been tested and developed to prevent or delay radiation-induced ocular pathology. Unfortunately, most of them have limited effectiveness or require doses that have significant side effects. As early as 1952, Von Sallmann et al. reported that topical or systemic administration of cysteine significantly delayed cataract formation in experimental animals irradiated with a 15 Gy ocular dose [89]. The use of cysteine

leads to a delay in mitosis in the lens epithelium and thus protects against the development of radiation cataracts. In contrast to the positive effects in the lens, with the administration of sulfhydryl compounds, in the conjunctiva, cornea and iris, protective effects after irradiation were not observed. Relatively more recent studies by Kobayashi et al., showed that 2- mercaptopropionylglycine and glutathione isopropyl ester (YM737) somewhat inhibited the progression of X-ray-induced cataracts in rats irradiated with 10 Gy [90, 91]. Reddy et al., administered 500 mg/kg amifostine before irradiation, which provided some protection against gamma-induced cataracts in experimental animals [92]. The exact mechanisms by which amifostine slows cataract formation are unknown. Some metalloporphyrins have the ability to neutralize free radicals. Studies by Mao et al. demonstrated that direct intraocular injection of the SOD mimetic MnTMPyP (Mn (III) tetrakis (1-methyl-4-pyridyl) porphyrin pentachloride) significantly reduced radiation-induced acute ocular inflammatory reactions and lens opacification in rats [93]. According to Sasaki et al., the SOD mimetic Tempol also reduced the severity of radiation-induced cataracts in rabbits after X-ray irradiation [94]. However, its rapid bio-reduction significantly limits its therapeutic use. Studies by Sezen et al. described the protective effect of carnitine administered at a dose of 200 mg/kg/day and vitamin E – 40 mg/kg/day on post-radiation retinal damage [95]. Long- term administration of Ginkgo biloba extract leads to a significant increase in the time for initial opacification of the lens after irradiation of experimental animals. Recently published studies show very conflicting results about the radioprotective effects of estrogens on eye structures. Hagemann et al. reported that topical eye pretreatment with 10% dimethylsulfoxide (DMSO) helped prevent complete lens opacification after 10 Gy x-ray irradiation of the head, but DMSO treatment after irradiation was completely ineffective [96]. Given the theory that the main target for radiation cataract is the germinal zone of the lens epithelium, DMSO has been suggested to transiently reduce DNA synthesis in it. Davis et al., described experiments in mice fed a Bowman-Birk protease inhibitor before and after irradiation, which resulted in a reduction in the prevalence and severity of radiation-induced lens opacities [97]. Studies by Kodama et al. show that a diet high in galactose (30%) reduces radiation-induced damage to the lens in experimental animals. The protective effect was observed whether the diet was started 1 week before or 1 week after irradiation [98]. The treatment of radiation retinopathy also remains limited and is a serious challenge for modern medicine. Photodynamic therapy, laser photocoagulation, oral pentoxifylline, intravitreal steroid therapy, and hyperbaric oxygen have inconclusive results and limited efficacy [99-112]. Anti-vascular endothelial growth factor agents (anti-VEGF agents) reduce vascular permeability and inhibit the formation of abnormal new vessels. Their application has also had variable results. Widely used are ranibizumab - an antibody fragment with good tissue penetration, blocking all forms of VEGF-A, and bevacizumab - a whole antibody with poorer tissue penetration but a longer half-life, also blocking all forms of VEGF-A. Anti-VEGF therapy involves continuous intravitreal injections at 1- to 3-month intervals with doses of 1.25 mg/0.05 mL, 2.0 mg/0.08 mL bevacizumab, or 0.5 mg/0.05 mL ranibizumab. They are useful in suppressing radiation-induced neovascular glaucoma, radiation maculopathy, and optic neuropathy. Some studies have shown improvement in radiation retinopathy and maculopathy after their administration [113-118]. Despite improvements in vision, discontinuation of anti-VEGF treatment often results in recurrence of macular edema and decline in visual acuity. In recent years, aflibercept has also been used. It is a human recombinant fusion protein that binds to and inhibits VEGF-A and placental growth factor (PIGF) activating receptors. Aflibercept has many times greater binding affinity for growth factors than other anti-VEGF agents (200 times greater affinity for VEGF than ranibizumab). One of the main advantages is the greater interval of the injections, which can be administered every 2 months. The recommended dose is 2 mg aflibercept, corresponding to 50 microliters (2 mg/0.05 ml) [119, 120]. It is believed that the corticosteroid preparation triamcinolone acetonide as well as the newer intravitreal implants - flucinolone acetonide reduce the production of VEGF, have an anti-inflammatory effect and prevent the disruption of the blood-retinal barrier. They have anti-angiogenic and anti-edematous effects, and the effect wears off over time [121, 122, 123]. Some studies have shown that intravitreal administration of triamcinolone acetonide (4 mg/0.1 ml) transiently reduces macular edema and improves visual acuity [107, 108, 109, 124]. Some corticosteroid implants containing 0.7 mg dexamethasone are promising [125, 126, 127, 128]. Further studies are needed to determine the sustainability of these results and whether the benefit of frequent injections outweighs the risks of glaucoma, cataracts, and endophthalmitis. Current research is aimed at preventing radiation retinopathy. Laser pan-retinal photocoagulation and intravitreal therapy with ranibizumab and bevacizumab are used preventively [129, 130, 131, 132, 133].

Discussion

The effects of ionizing radiation on the eye were first described by the end of the 19th century. The first scientific reports describing the effects of ionizing radiation on the eye came around the time of the Second World War. Early damage mainly affects the rapidly proliferating epithelial cells and occurs during the course of irradiation or several weeks after. Blepharitis, conjunctivitis and keratitis usually develop. Late radiation-induced damages develop after a latent period of several months to tens of years, depending on the individual biological characteristics and the absorbed dose. These changes are mainly due to endothelial damage and microcirculatory dysfunction or to genomic damage to epithelial cells that do not die immediately after irradiation but have the potential to divide and differentiate, as in radiation cataract. Typical late radiation-induced injuries are cataracts, radiation retinopathy, and radiation-induced optic neuropathy. Radiation-induced eye injuries turn out to be common and sometimes unavoidable complications of radiotherapy but should also be anticipated as a result of radiation accidents and possible radiological terrorism. Some problems are apparent here: the knowledge of most medical personnel on radiation-induced injuries, including eye injuries, is limited; prevention and treatment options are also limited and with somewhat unconfirmed effect. We came to some conclusions which follow.

Conclusions

Radiation-induced damage to the eye is a common and sometimes unavoidable complication of both radiotherapy and radiation accidents. Reducing their frequency is possible by enriching our knowledge about radiation tolerance of eye structures, risk factors, pathogenetic mechanisms, clinical picture, prevention and treatment measures. A more active and detailed study of pathogenesis, immunological and pathophysiological changes is needed in order to introduce new approaches in therapy. More prevention and treatment options are necessary and research into them should be accelerated.

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