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ORIGINAL ARTICLE

Magnetic resonance diffusion tensor imaging study of rhesus optic nerve radiation injury caused by a single dose/fractionation scheme stereotactic radiosurgery at an early stage

Shuang Min Fan[a,1], Wei Chen[a,1], Li Xiong[b], Yong Xia[a], Yue Bin Xie[a], Jing Chen[a,*]

[a] *Department of Neurosurgery, Sichuan University, West China Hospital, Chengdu, Sichuan Province, PR China*

[b] *Department of Neurosurgery, Sichuan Provincial People's Hospital, Chengdu, Sichuan Province, PR China*

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KEYWORDS
Radiation-induced optic neuropathy;
Radiosurgery;
Diffusion tensor imaging;
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Summary

Background and purpose: Radiation-induced optic neuropathy (RION) is a devastating late complication of radiotherapy. However, research on the imaging performance of RION is not sufficient. The aim of this study was to investigate the performance of magnetic resonance diffusion tensor imaging (DTI) early after injury of the optic nerve of rhesus monkeys by a single-dose/fractionation-scheme of stereotactic radiosurgery (SRS).

Materials and Methods: The intraorbital optic nerve contour of 5 rhesus monkeys was acquired by magnetic resonance imaging (MRI). Then, the unilateral intraorbital optic nerves of 5 rhesus monkeys were injured by gamma knife surgery (GKS) with a single-dose/fractionation scheme (marginal dose of 15 Gy, 50% isodose curve). DTI was performed before the irradiation and 1 week, 2 weeks, 4 weeks, and 24 weeks after injury to obtain the cross-sectional area, and the fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD) and radial diffusivity (RD) values.

Abbreviations: SRS, stereotactic radiosurgery; GKS, gamma knife surgery; RION, Radiation-induced optic neuropathy; AVP, anterior visual pathways; MRI, magnetic resonance imaging; DTI, magnetic resonance diffusion tensor imaging; AD, axial diffusivity; RD, radial diffusivity; FA, fractional anisotropy; ADC, apparent diffusion coefficient; TR, repetition time; TE, echo time; FOV, field of view; ROI, region of interest; mfVEP, multifocal visual evoked potentials.

* Corresponding author at: Department of Neurosurgery, Sichuan University, West China Hospital, Chengdu, Sichuan Province, PR China. Tel.: +86 13708182813.

E-mail address: chenjing6811@126.com (J. Chen).

[1] The first two authors contributed equally to this paper.

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Results: The cross-sectional area of the injured optic nerve exhibited significant atrophy 24 weeks after SRS. FA declined 1 week after injury; this value then increased slightly but remained lower than before injury ($P < 0.05$). AD began to decline in the 2 weeks after injury and gradually disappeared ($P < 0.05$).
Conclusion: SRS with a single-dose/fractionation scheme (marginal dose of 15 Gy, 50% isodose curve) on the unilateral intraorbital optic nerve can induce RION. DTI can detect RION at an early stage. FA and AD are useful indicators for RION diagnosis. In the early stage, the primary site of RION may be the vascular endothelium.

Introduction

The complete removal of tumors in or adjacent to the optic nerve, including at the suprasellar, cavernous sinus, optic nerve sheath, and optic canal regions, may cause visual impairment and even loss of vision due to direct or indirect optic nerve injuries, and stereotactic radiosurgery (SRS) may be appropriate for addressing tumors of or near the optic nerve or as an adjuvant treatment for residual tumors [1—4]. Gamma knife surgery (GKS) is an SRS technique that is widely used to treat intracranial tumors, vascular malformations and orbital tumors. However, when performed in or near the optic nerve, the ray to kill or control the growth of tumors will injure the optic nerve. Radiation-induced optic neuropathy (RION) is a devastating late complication of radiotherapy of the anterior visual pathway that results in acute, profound, irreversible visual loss. Once the loss of vision occurs, the prognosis is poor despite treatment [5]. Early detection of RION is beneficial because expedient treatment can reduce damage [6,7]. One study reported that the incidence of RION was 0% to 2.6%, 0% to 4.7%, and 0% to 13.9% for patients receiving a single dose/fractionation scheme of SRS on the anterior visual pathways (AVP) with 8 Gy, 10 Gy, and 12 Gy, respectively [8], while another study reported that the incidence of RION was 0, 0, 0, and 10% for patients receiving a single-dose/fractionation scheme of SRS on the AVP with $\leq$ 8 Gy, 8.1—10.0 Gy, 10.1—12.0 Gy, and > 12 Gy, respectively. The overall risk of RION in patients receiving > 8 Gy to the AVP was 1.0% [9]. The actuarial incidence of optic neuropathy was zero for patients who received a radiation dose of less than 10 Gy, 26.7% for patients receiving a dose in the range of 10 to less than 15 Gy, and 77.8% for those who received doses of $\geq$ 15 Gy [10]. Moreover, a single-dose/fractionation scheme of SRS with a marginal dose of 15 Gy on a 50% isodose curve was sufficient to lead to RION [11]. A recent study has shown that hyperfractionation (two or more than twice-daily radiotherapy sessions) may reduce the risk of developing RION [12]. A relationship between the dose of radiation and latency of symptom onset has been proposed, with shorter latency at higher doses [5].

Compared with conventional magnetic resonance imaging (MRI), magnetic resonance diffusion tensor imaging (DTI) is more sensitive for detecting the microstructure of a white matter injury. DTI can measure the microstructure within tissues based on differences in the directions of water molecule movements [13,14]. DTI is increasingly being applied to central nervous system research, including studies of demyelinating diseases, ischemic disease, tumor radiation necrosis, and traumatic brain injury [15]. In DTI, the axial diffusivity (AD) value (diffusion along the nerve fibers) and radial diffusivity (RD) value (diffusion across the nerve fibers) are closely correlated with axonal and myelin damage, respectively [16—18].

To induce RION within a short time frame, we randomly administered a radiation dose to the unilateral intraorbital optic nerve with a marginal dose of 15 Gy on a 50% isodose curve. Although the dose in this study was higher than the routine dose for the optic nerve in clinical practice, this dose insured the occurrence of RION, thereby allowing the observation of changes in DTI at an early stage of RION. We protected the optic chiasm and contralateral optic nerve from a 3-Gy radiation dose. Our study focused on the changes in DTI, specifically in the fractional anisotropy (FA), apparent diffusion coefficient (ADC), AD, and RD values. In addition, we also evaluated the cross-section of the optic nerve and discussed the occurrence, development, and early diagnosis of RION.

Materials and methods

Animal preparation

Six- to eight-year-old healthy rhesus monkeys ($n = 5$) with a mean body weight of 8 kg were obtained from Ping An Animal Breeding and Research Base (Chengdu, China). All animal experiments were approved by the Ethics Committee of Sichuan University. Throughout the study, the monkeys were housed individually under constant temperature (20—22 °C) and humidity (65%) with an 11-h light cycle (light 07:00—18:00) in a room permitting visual, auditory, and olfactory contact with other monkeys in accordance with NIH Guidelines for the Care and Use of Laboratory Animals (1996). Before the GKS and 1, 2, 4 and 24 weeks after injury, anesthesia was induced by intramuscular injection of ketamine (10 mg/kg) and maintained by continuous intravenous infusion of pentobarbital (6—9 mg/kg/h).

Gamma knife radiosurgery

A Leksell G stereotactic head frame (Elekta Instruments AB, Stockholm, Sweden) was fixed to the anesthetized monkey's head, and MRI was performed. The MRI images were transferred to the Leksell GammaPlan® version 9.0 (Elekta Instruments AB, Stockholm, Sweden). Then, the contour of the intraorbital optic nerve was acquired from