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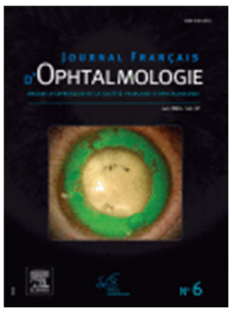

Prospective assessment of peripapillary microvasculature using optical coherence tomography angiography in para-optic intracranial and sinonasal tumors treated with proton therapy

Évaluation prospective de la microvascularisation péripapillaire à l'aide de l'angiographie par tomographie en cohérence optique dans les tumeurs intracrâniennes et sinonasales para-optiques traitées par protonthérapie

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Summary

Purpose

Radiation-induced optic neuropathy (RION) is rare but may lead to blindness. The mechanisms by which this occurs include endothelial and neuronal damage, but RION has been assessed very little in the case of extraocular tumors treated with high-energy proton therapy, the use of which is expanding worldwide. We assessed peripapillary microvascular changes by optical coherence tomography angiography (OCT-A) in patients undergoing high-energy proton therapy for para-optic intracranial or head and neck tumors.

Materials and Methods

In this prospective institutional review board approved study, patients receiving > 40Gy_RB□maximal PBT dose to their optic nerve between 2018 and 2020 underwent quantitative OCT-A analyses. ImageJ software was used to assess changes in the peripapillary superficial vascular complex (SVC) using vascular area density (VAD), vessel length density (VLD) and fractal dimension (FDsk). Uni- and multivariate analyses were performed.

Results

Of 47 patients (78 eyes) with 29 ± 6 months of follow-up (range 18–42), 29 patients (61.7%) had previously undergone surgery and 18 (32.1%) had microvascular abnormalities prior to proton therapy. Total radiotherapy dose was the most relevant factor in decreased peripapillary microvasculature. Duration of follow-up was associated with lower VAD (P = 0.005) and mean retinal nerve fiber layer (RNFLm) thickness also decreased. There was no significant correlation between OCT-A changes and mean visual defect.

Conclusion

Peripapillary microvasculature changes may occur from tumor compression or surgery and proton therapy for extraocular tumors. OCT-A may provide quantitative and mechanistic insights into RION before the occurrence of clinical symptoms.

Résumé

Objectif

La neuropathie optique radio-induite (RION) est rare mais peut conduire à la cécité. Ses mécanismes incluent des dommages

endothéliaux et neuronaux, mais la RION a peu été évaluée pour les tumeurs extra-oculaires traitées par protonthérapie à haute énergie, dont l'utilisation se développe dans le monde entier. Nous avons évalué les changements microvasculaires péripapillaires chez les patients traités par protonthérapie de haute énergie pour des tumeurs para-optiques intracrâniennes ou de la tête et du cou, en utilisant l'angiographie par tomographie en cohérence optique (OCT-A).

Méthodes et matériel

Dans cette étude prospective approuvée par le Comité de révision institutionnel, les patients ayant reçu > 40Gy_RB□dose maximale de PBT sur leur nerf optique entre 2018 et 2020 ont fait l'objet d'analyses quantitatives OCT-A. Le logiciel ImageJ a été utilisé pour évaluer les changements du complexe vasculaire superficiel péripapillaire (SVC) en utilisant la densité de la surface vasculaire (VAD), la densité de la longueur des vaisseaux (VLD) et la dimension fractale (FDsk). Des analyses uni et multivariées ont été réalisées.

Résultats

Sur 47 patients (78 yeux) avec un suivi de 29 ± 6 mois (intervalle 18–42), 29 patients (61,7 %) avaient déjà subi une intervention chirurgicale et 18 (32,1 %) présentaient des anomalies microvasculaires avant la protonthérapie. La dose totale de radiothérapie était le facteur le plus important dans la diminution de la microvascularisation péripapillaire. La durée du suivi a été associée à une diminution de la VAD (p = 0,005) et la couche moyenne de fibres nerveuses rétiniennes (RNFLm) a également diminué. Il n'y avait pas de corrélation significative entre les changements OCT-A et le déficit visuel moyen au champ visuel.

Conclusion

Des altérations de la microvascularisation péripapillaire peuvent survenir à la suite d'une compression tumorale ou d'une chirurgie et d'une protonthérapie de tumeurs extra-oculaires. L'OCT-A peut fournir des informations quantitatives et mécanistiques sur les RION avant l'apparition des symptômes cliniques.

Introduction

Radiation-induced optic neuropathy (RION) can start insidiously and remain undetected until it leads to blindness [1]. It is rare, with a peak at 18 months with onset varying from 3 months to 8 years after irradiation, depending on radiation modality. Short latency has been associated with high total dose and high dose per radiotherapy fraction as performed in peripapillary melanomas treated with dedicated low-energy ocular proton therapy or in extraocular tumors abutting the optic nerve and treated with conventional radiotherapy using photons (as tridimensional, intensity-modulated and stereotactic body radiotherapy) [2].

Due to its ballistic advantages, high-energy proton therapy has a prominent place in the treatment of intracranial, head, and neck tumors surrounded by organs at risk (OAR) [3]. In such tumors, the prevalence of RION is in the order of 6% [4]. The risk is higher in tumors abutting to the visual pathways since radiotherapy can affect the optic nerve adjacent to the tumoral target. Data concerning radiation-induced effects on the optic nerve after high-energy proton therapy for extraocular tumors are limited, usually retrospective, and mostly limited to photon-based radiotherapy techniques. They often rely upon clinical detection at a stage where RION is unlikely reversible. Preliminary studies suggest that paraclinical examinations, such as visual evoked potentials, may be helpful in early RION detection, with some potential for recovery [5], [6]. However, the pathophysiological mechanisms underlying nerve damage, detected by visual evoked potentials, are not entirely understood. RION might be due to direct lesions by axonal injury, to demyelination by progressive neurodegeneration, or to indirect lesions by ischemic vasculopathy [7], [8], [9].

Optical coherence tomography angiography (OCT-A) is a rapid and non-invasive technique for imaging vasculature in the eye at the macular and peripapillary scales. Very few studies have assessed peripapillary OCT-A changes after irradiation and none after extraocular proton therapy [10], [11], [12], [13].

Both high-energy proton therapy and tridimensional and intensity-modulated photon-based radiotherapy deliver fraction sizes of about 2Gy_RB□(relative biological effectiveness) given 30 times for up to 70Gy_RB□in six to eight weeks using multiple beams. They are used in similar tumor types and may similarly result in optic nerve damage instead of damage to intraocular structures. In contrast, uveal melanomas are treated with a small single beam of extremely hypofractionated proton therapy delivering 4 to 5 fractions of about 15Gy_RB□each up to 70Gy_RB□in a single week. Studies based on uveal melanomas might serve as cautious comparators, as a considerable amount of data is available for these tumors. However, outcomes of extraocular tumors treated with high-energy proton therapy cannot be directly extrapolated from data observed for intraocular tumors and one must account for the different radiotherapy fractionation schemes and dose distribution on the optic nerves.

The aim of this study was to identify changes of the vessel area density, vessel length density, and fractal dimension of the peripapillary microvascular network using OCT-angiography (OCT-A), as a surrogate for RION secondary to extraocular proton therapy. We also intended to determine whether these post-radiation changes occurred more frequently in patients with peripapillary microvascular changes before radiation. Secondary objectives were correlations between differences between OCT-A parameters and patient, eye, tumor and treatment characteristics, as well as correlations between OCT-A and retinal fiber layer thickness and visual defect.

Section snippets

Population

We performed a prospective, observational, single-center cohort study at the Ophthalmology department of the University Hospital of Caen, in France. The study was approved by the institutional review board of Caen University Hospital (France) ID 3464 and was in accordance with the tenets of the Declaration of Helsinki. High-energy PBT was performed for all patients at the CYCLHAD center

in Caen, with a cyclotron ProteusOne® (IBA, Louvain la Neuve, Belgium). The treatment was delivered in

Population

Seventy-eight eyes of 48 patients were included. There were 68.1% women and 31.9% men. Mean age was 58 ± 14 years (range 24–87 years). The most common histological type of tumor was meningioma (48.9%), followed by pituitary macroadenoma (23.4%) and 13 had 9 other tumor histological types. Most of the patients had undergone at least one prior tumor surgical resection procedure (61.7%). Few patients underwent chemotherapy concomitant with adjuvant proton therapy (6.4%). Three-quarters of the

Discussion

Until the advent of OCT-A, the analysis of retinal vasculature stratified by layer was limited. OCT-A provides a noninvasive and sensitive visualization of retinal vessels and not only allows a qualitative but also quantitative evaluation [16]. It is studied in maculopathy and retinopathy of different origins including radiotherapy. Papillary OCT-A first demonstrated its value in glaucoma by showing that vessel density is lower in glaucoma patients compared with healthy controls [17]. Since

Conclusion

Proton therapy induces delayed peripapillary microvasculature changes in patients irradiated for para-optic tumors. Of note, one third of the patients already had optic nerve damage as observed by papillary OCT-A alterations that were likely due to tumor compression or surgery before proton therapy in these patients selected with para-optic tumors. There was no additional deterioration OCT-A in this patient's sub-population.

Our study suggests promising preliminary evidence that papillary-OCT-A

Disclosure of interest

The authors declare that they have no competing interest.