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Mechanisms of phosphene generation in ocular proton therapy as related to space radiation exposure

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ABSTRACT

Particle therapy provides an opportunity to study the human response to space radiation in ground-based facilities. On this basis, a study of light flashes analogous to astronauts' phosphenes reported by patients undergoing ocular proton therapy has been undertaken. The influence of treatment parameters on phosphene generation was investigated for 430 patients treated for a choroidal melanoma at the proton therapy centre of the *Institut Curie* (ICPO) in Orsay, France, between 2008 and 2011. 60% of them report light flashes, which are predominantly (74%) blue. An analysis of variables describing the patient's physiology, properties of the tumour and dose distribution shows that two groups of tumour and beam variables are correlated with phosphene occurrence. Physiology is found to have no influence on flash triggering. Detailed correlation study eventually suggests a possible twofold mechanism of phosphene generation based on (*i*) indirect Cerenkov light in the bulk of the eye due to nuclear interactions and radioactive decay and (*ii*) direct excitation of the nerve fibres in the back of the eye and/or radical excess near the retina.

1. Introduction

Since the beginning of manned space exploration, anomalous light flashes called *phosphenes* have been widely reported by astronauts, especially during Apollo missions and on board space stations (Fuglesang et al., 2006; Pinsky et al., 1974). Predicted by Tobias (1952) for high altitude flights, these percepts are thought to be due to cosmic rays interacting with the human visual system or brain. Observations from the *SilEye2* experiment on board the Mir space station suggested two complementary explanations for phosphene inducement: direct excitation of the retina by heavy nuclei and interaction of secondary particles produced by protons with the eye (Casolino et al., 2003). Ground-based experiments in particle accelerators were likewise carried out in the 1970s in order to study phosphene occurrence under controlled conditions (Narici, 2008). They showed that Cerenkov radiation was also a cause of anomalous visual perceptions comparable to those described by astronauts, for it was compatible with both the kinetic energy of the particles and the estimated threshold sensitivity of the retina (McNulty et al., 1975). Nevertheless, the details of phosphene generation mechanisms remain poorly understood, just as the specific role of protons. Although experiments by Gramenitskii and Fetisov (1987) confirmed the occurrence of Cerenkov light flashes induced by 1860 MeV protons, the extent to which they can trigger phosphenes is still somewhat unclear (Avdeev et al., 2002; Narici, 2008). Indeed, the number of flashes reported by astronauts passing through the South Atlantic Anomaly (SAA), a portion of the Earth's inner radiation belt where most of the flux is composed of low-energy protons, has been found to vary considerably from one mission to another. In some cases, phosphene occurrence is significantly enhanced in the SAA (Casolino et al., 2003; Pinsky et al., 1975; Rothwell et al., 1976), while in others no increase is observed (Budinger et al., 1977). Further investigations are therefore highly warranted, particularly given that protons are the most abundant cosmic rays.

In this respect, the development of medical treatments using proton beams represents a great opportunity to study their interaction with the human visual system. Indeed, protons have recently been found to produce phosphenes in medical facilities whose maximum energy available is always far below the Cerenkov threshold (about 485 MeV in the eye's vitreous humour of refractive index $n = 1.33$). In particular, 73 MeV protons

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have been found to induce light flashes in patients treated for ocular cancers at the *Institut Curie* in France (Khan et al., 2010). This was the first time such low-energy protons were reported as phosphene inducers in a ground-based survey since previous informal reports from another proton therapy centre indicated that patients did not perceive flashes (Sannita et al., 2006). These proton-induced phosphenes were thought to be more likely caused by interaction of primary protons with the eye (e.g. by generating radicals very close to the retina (Narici et al., 2009)) than by possible Cerenkov radiation due to secondary particles. Indeed, secondary Coulomb electrons cannot produce Cerenkov light with a primary beam under 120 MeV (Helo et al., 2014). However, non-elastic nuclear interactions and radioactive decay were recently suggested to be responsible for some indirect Cerenkov emission during proton therapy (Helo et al., 2014).

In this context, providing a framework able to trace the possible mechanisms of phosphene generation in ocular proton therapy would be valuable. To this end, an analysis of proton-induced light flashes has been undertaken with a larger number of cases and a more advanced correlation study than in previous works (Khan et al., 2010) in order to relate treatment parameters to phosphene generation.

2. Protocol

The present study is based on anonymous data from 430 patients treated for a choroidal melanoma at the proton therapy centre of the *Institut Curie* (ICPO) in Orsay, France, between 2008 and 2011.

Before the treatment, patients undergo eye surgery in order to suture radio-opaque tantalum clips on the sclera around the tumour base (Dendale et al., 2006). The treatment itself then consists of four sessions each of about 1-min duration, taking place over four consecutive mornings. A 200 MeV synchrocyclotron and then, as from 2010, a 235 MeV cyclotron are used to produce the therapeutic proton beam. Beam energy is first reduced to 75 MeV through a beryllium degrader and then adapted to the tumour size and location using a polycarbonate binary filter located 2 m ahead of the patient. It finally ranges from 40 to 65 MeV, with a typical value about 55 MeV (Khan et al., 2010), and it is modulated to get a homogeneous dose distribution over the tumour. The synchrocyclotron operated at 450 Hz, causing the beam to be emitted in 20 μs long pulses, each separated by $\sim$ 2.2 ms. Within each pulse, beam intensity was typically constant at $\sim 10^{10}$ protons per second. The cyclotron that replaced it in 2010 operates at 106 MHz, producing a continuous beam. The dose delivered during each session is 13.64 Gy (15 Gy RBE, assuming a relative biological effectiveness (RBE) of 1.1).

The position of the patient's eye is carefully chosen in order to preserve, where possible, the lacrimal gland, the eyelids, the optic disc and the macula. The patient is thus immobilized using custom-made mask and bite block so that they hold this exact same position during all four sessions. Eyelid retractors keep the eye open during irradiation. A camera is used to monitor eye position from outside the treatment room. It is illuminated by infrared LEDs as all visible lights are switched off at least 15 min before irradiation (except one little flashing red LED used to keep the gaze angle constant). A dazzling red light is turned on for a few seconds in order to control the beam position at least 2 min prior to irradiation.

Throughout the study period, patients were given a 9-item questionnaire at the end of each session regarding their potential anomalous perceptions during irradiation. Data from the treatment planning system (TPS) and anonymised patient biodata were also collected, representing a final dataset of 97 variables for each patient. To facilitate the analysis, variables which can be correlated with questionnaire replies have been grouped into 13 parameters listed in Table 1.

Table 1
Table of parameters correlated with phosphene occurrence.

Parameter	Number of correlated variables
Physiology	0/10
Tumour size	4/4
Tumour location	2/4
Beamline parameters	0/4
Irradiation duration	0/4
Irradiated fraction of the retina	1/3
Irradiated fraction of the eyeball	5/6
Irradiated fraction of the crystalline lens	6/6
Irradiated fraction of the ciliary body	2/3
Irradiated fraction of the optic disc	1/3
Irradiated fraction of the optic nerve	1/3
Irradiated fraction of the macula	0/3
Irradiated fraction of the tumour	0/3
Total	**22/56**

3. Results

Information about the past medical history of 406 patients over 430 is available from the ICPO anonymous database. In order to avoid any possible bias, only those who had no history of phosphenes prior to their treatment are considered in this study. This corresponds to 225 patients (52%). Among them, 137 (60.9 $\pm$ 3.3%) report at least one light flash during at least one of the four treatment sessions. It should be noted that this result is very robust as it remains almost unchanged when all 430 patients are included (59.5 $\pm$ 2.4%). 57.3 $\pm$ 4.3% of the patients reporting phosphenes see flashes during all four sessions. This corresponds to 34.2 $\pm$ 3.2% of all the patients.

On average, patients perceiving phosphenes report about 3 light flashes per session. This value should be considered with caution as it is likely underestimated since it is very difficult for patients to accurately count light flashes. Indeed, many of them only report "several" flashes without any further detail. Flashes are predominantly seen in the left eye (59.9 $\pm$ 1.5%) whereas only 48% of the patients had their left eye treated. Again, this is to be regarded with caution because patients can only answer the question with little accuracy. A large majority (73.8 $\pm$ 1.4%) of the flashes are described as a blue light. No other anomalous sensory perception (smell, taste, touch or hearing) is reported, contrary to what was observed at the Loma Linda proton therapy centre (Narici et al., 2010).

Among the 56 variables describing the patient's physiology, properties of the tumour and dose distribution, 22 are found to be correlated at two-sigma level (95.5%) with phosphene occurrence (Table 1). It should be noted that none of them is related to physiological parameters (age, gender, height, weight or eye anatomy), nor to the macula although it corresponds to the largest concentration of cone cells in the eye.

A detailed analysis shows that variables correlated with phosphene occurrence can be divided into two independent groups of correlated parameters. A first group of three variables includes the distance between the tumour and the optic disc and the fraction of the dose received by the optic disc and the optic nerve. Another group of 18 variables includes the tumour size and the fraction of the dose received by the retina, the eyeball, the crystalline lens and the ciliary body. The number of patients reporting phosphenes and the number of those that do not are displayed as a function of one typical parameter from each group in Fig. 1.

These results indicate that the more the optic disc is irradiated, the more light flashes are observed: when 80–100% of the optic