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RETINAL DISORDERS

Slowing the degenerative process, long lasting effect of hyperbaric oxygen therapy in retinitis pigmentosa

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Abstract
Background Retinitis pigmentosa (RP) therapy is still an unsolved challenge. Recent reports have underlined that hyperbaric oxygen (HBO) therapy could play a role in slowing the retinal degenerative process. The aim of this study was to assess the efficacy of HBO therapy on visual function in RP patients.
Methods We performed a single-center, comparative, longitudinal case-controlled randomized clinical trial, which lasted 10 years. We randomly divided RP patients into two groups. Group 1, the control group, consisted of 44 RP patients (21 males and 23 females; mean age 35.5) who took Vitamin A. Group 2, with 44 RP patients (21 males and 23 females; mean age 35,02), underwent HBO therapy. No statistically significant difference was found at the beginning of the study between the two groups. We compared the results concerning visual acuity, Goldmann perimetry, static perimetry Humphrey field analyzer (HFA), and electroretinogram (ERG) obtained in the two groups at 5 and 10 years follow-up. Statistical analysis was performed with Kaplan-Meier life-table with the evaluation of log-rank coefficient.
Results At 5 year follow-up, 87.5% of group 2 patients preserved 80% of the initial visual acuity, while the same result was achieved in only 70.4% of group 1 patients (X^2= 8.2; $p<0.01$); at 10 year follow-up, 63.33% of group 2 patients preserved 80% of the initial visual acuity, while the same percentage of residual visual acuity was maintained in 40% of group 1 patients ($X^2=3.22$; $p=0.05$). At 10 year follow-up, Goldmann perimetry (target I4e) did not change in 31.6% of group 2 and in 10.5% of group 1; evaluation of mean defect (MD) with static perimetry HFA showed that 53% of HBO patients had 80% of residual mean sensitivity compared to 23.5% of the control group patients ($X^2=4.72$; $p=0.035$). ERG b-wave mean values at the end of the protocol were significantly higher in the HBO treated group ($X^2=4.53$; $p=0.013$).
Conclusion Our study underlines that HBO therapy can be a safe alternative approach to RP patients, contributing to the stabilization of their visual function concerning visual acuity, visual field, and ERG responses while waiting for a definite cure.

Keywords Retinitis pigmentosa · Hyperbaric oxygen therapy · Retina

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Introduction

Retinitis pigmentosa (RP) is a group of clinically and genetically heterogeneous retinal degenerations characterized by chronic progressive loss of rod and cone function [1]; photoreceptor damage is actually explained with an invalid gene product or protein causing metabolic wrong

step in the photo-transduction process [2, 3]. Different inheritance patterns of tapetoretinal degenerations were described: autosomal dominant, recessive, and X-linked, and all of them are associated with point mutations and intragenic microdeletions as well as other molecular defects within over 20 different RP loci.

Several genes underlying autosomally inherited forms were identified by candidate gene approaches, including genes coding for rhodopsin and other proteins [4]. All these gene defects may lead to the presence of a qualitative or quantitative altered protein, thus permitting premature cell death or apoptosis. In the RP rod system, damage is more prominent, so that effects on central vision are variable, and some patients can maintain good visual acuity throughout their lives despite extinguished electroretinogram and visual field reduction [5]. The way visual acuity changes with age is important in this disease, but the course of visual loss in RP has never been clearly established [6].

Hyperbaric oxygen (HBO) therapy, as previously described in our study [7], seems to be able to modify the progression rate in RP.

Our aim was to assess its role and usefulness in a long lasting period, evaluating its efficacy on rescuing retinal photoreceptors and preserving visual function.

Materials and methods

We began treating RP patients with HBO in 1982. Preliminary data were carried out to assess if HBO had positive effects (1982–1984). Our studies were addressed to tune the best treatment protocol (1984–1988); then, a national treatment protocol was approved by the Italian National Committee for Hyperbaric Medicine.

In 1995, we randomly enrolled 120 RP patients who had come to the Inherited Degenerative Retinal Disease Unit, at the Policlinico Umberto I, University "La Sapienza" of Rome. We divided patients into two groups of 60 patients: group 1 (control group) was treated with vitamin A, group 2 (case group) with HBO.

The diagnosis of RP was based on a case history of slow and progressive reduction of visual acuity with nictalopia, progressive reduction of peripheral visual field documented by manual perimetry, or conventional perimetry by HFA (Humphrey 10-2 program, Goldman III stimuli, Sita Standard strategy on 68 points) typical ERG, visual evoked potential (VEP) changes, chorioretinal pigment migration, thinning of the retinal vessels, optical sub-atrophy, and typical vitreal modifications. Inclusion criteria were: patients with clearly hereditary RP (we performed genetic analysis on all patients for rhodopsin and peripherin genes; only four patients with autosomic dominant RP showed point mutation: 3 on codon 135 and 1 on codon 347); best corrected visual acuity (BCVA) ≥0.50 logMAR; visual field ≥3 degree diameter circle; and recordable ERG. Exclusion criteria were: patients with sporadic RP; BCVA ≤0.50 logMAR; visual field ≤3 degree diameter circle; and unrecordable ERG. These criteria were chosen as having a good chance to record a significant change of visual performance. At the time of selection there was no statistically significant difference concerning mean visual acuity, Goldmann perimetry, conventional perimetry Humprey (HFA 10-2), and ERG max amplitude between the two groups.

Informed consent to participate in the study was obtained from all the patients. The ethics committee of our institution approved the study protocol. All the procedures adhered to the tenets of the Declaration of Helsinki. Informed consent to participate in the study was obtained from all the patients.

At 10-year follow-up (2005), group 1 (control) consisted of 44 patients (88 eyes), 21 males and 23 females, aged between 13 and 61 years (mean age 35.5±14.3). Forty-one presented typical RP (rod-cone dystrophy), one patient Usher syndrome, and two patients cone-rod dystrophy.

Group 2 was reduced, because of the presence of systemic disorders that contra-indicate HBO therapy, to 44 patients (88 eyes) composed of 21 males and 23 females, aged between 18 and 71 years (mean age 35.02±5.6). Thirty-three of them presented typical RP (rod-cone dystrophy), six patients Usher syndrome, and five patients cone-rod dystrophy.

At the beginning of the study we performed a complete ophthalmologic examination of all patients according to the following scheme:

- Assessment of distant and near BCVA with a Snellen chart [8]; decimal results were converted to logMAR
- Grading of lens opacities by slit- lamp biomicroscopy according to the criteria proposed by Fishman and modified by Pannarale et al. [9]. Six progressive grades were adopted evaluating the concentric extension of the opacities from the axial area. Cataract surgery was performed at step 6
- Grading of vitreal aspects at slit-lamp biomicroscopy according to our previous study [10]
- Fundus examination by indirect binocular ophthalmoscope and slit lamp biomicroscopy to assess central and/or mid-peripheral retinal changes. The aspects of the optic disc and the retinal vessels were particularly evaluated
- Visual field examination with Goldmann perimetry with III-4 and I-4 targets moving from nonseeing to seeing areas and vice versa
- Conventional perimetry by Humphrey field analyzer (HFA) (Carl Zeiss Meditec, Inc, Dublin, California,

USA) (Humphrey 10-2 program, Goldman III stimuli, Sita Standard strategy on 68 points) evaluating whole mean defect (MD)
– Electroretinographic analyses were performed according to ISCEV standards evaluating maximum amplitude (a–b wave) as previously described [11]; until 2000 ERGs were recorded with the Conel BDC instrument (Rome, Italy), then after that time a MetroVision (France) ERG device was used

All the above-mentioned examinations but ERG (performed at one, two, three, five, and ten years) were repeated twice a year with the interval of approximately 6 months. All examinations were performed during routine testing sessions where the examiner was unaware if the patient was selected for HBO or not. Maximal ERG responses were recorded according to our low-noise methods. Briefly, 100 iterations, elicited with a 10 μs standard flash from dark-adapted eye (after full pupillary dilation and 20 min dark adaptation) with a full-field 20-lux/s 0.5 Hz flash stimulation, were recorded and off-line averaged in order to evaluate the retinal response. Henkes-type corneal electrodes, connected to a mechanical, continuously controlled suction pump, were employed to record the tracings. In cases of extreme reduction of the signal, a "differential derivation" system was used (electrode on the patched fellow eye used as a reference) resulting in a substantial increase in the signal-to-noise ratio.

Amplitude of the signal and a-wave and b-wave peak time were determined according to standard criteria [12]. ERG b-wave amplitudes were expressed and statistically analyzed both as row data (in microvolts μV) and after conversion to log units, and peak times were determined in milliseconds. Results can be seen in Fig. 3.

Therapeutic scheduling of hyperbaric oxygen therapy was reported in our previous paper [7]. Group 2 patients underwent hyperbaric oxygen exposure for 90 min (2.2 absolute atmosphere or 12 m undersea) to avoid both the toxic effect of high levels of oxygen (vasoconstriction) and worsening of photoreceptor rescuing due to too much time between each delivery. There were three sessions, as standard procedure, 5 days a week in the first month, 5 days consecutively a month for the following 11 months, and 5 days consecutively every 3 months for the following 9 years as stated by the Italian National Committee for Hyperbaric Medicine.

Statistical analysis was performed with the Kaplan-Meier life table with the evaluation of log-rank coefficient. We described the difference between the two groups in visual acuity loss, Goldmann perimetry, conventional perimetry by HFA (Humphrey 10-2 program, Goldman III stimuli, Sita Standard strategy on 68 points), and ERG at 5 and 10 years follow-up.

Patients cut-off and negative event were considered when visual acuity and MD were 20% less than the baseline.

Results

Posterior subcapsular opacities

At baseline, 76 eyes (86.36%) of the HBO group and 72 eyes (81.81%) of the control group showed posterior subcapsular opacities graded from grades 1–6 of the Fishman scale for posterior subcapsular cataract modified by Pannarale [9]. Twenty-one eyes (26.92%) from the HBO group and 17 eyes (23.61%) from the control group underwent cataract surgery while participating in the study. These values were not statistically significant and were not analyzed further.

Nd:YAG laser posterior capsulotomy rates

At 6 and 12 months after cataract surgery, the incidence of Neodymium:YAG (Nd:YAG) laser posterior capsulotomy was 63% and 87% in the HBO group and 65% and 86% in the control group, respectively. These data were not statistically relevant and were not analyzed further in the study.

Vitreal aspects

The main aspects in the HBO group were floating cotton-ball-like condensations (26.824%) associated with fibrillary degeneration (15.88%), nonpigmentary vitreal particulation in 26.60% of eyes, and the pigmentary type in 12.017%. Posterior vitreal detachment was detected without any other vitreal alteration in only 0.43%, while 18.24% of examined eyes showed no vitreal alterations.

The main aspects in the control group were floating cottonball-like condensations (27.01%) associated with fibrillary degeneration (14.94%), and nonpigmentary vitreal particulation was detected in 26.69% of eyes with the pigmentary type in 13.018%. Posterior vitreal detachment was detected without any other vitreal alteration in only 0.41%, while 17.84% of examined eyes showed no vitreal alterations. No statistically significant change was detected in both groups during the study.

At 5 years follow-up, 87.5% of patients treated with HBO preserved 80% of the initial visual acuity, while the same percentage of residual visual acuity was preserved in only 70.4% of group 1 as shown in Fig. 1. To compare these results the log-rank test was used ($X^2=8.2$; $p<0.01$).

At 10 years follow-up, 63.33% of patients treated with HBO preserved 80% of the initial visual acuity, while the

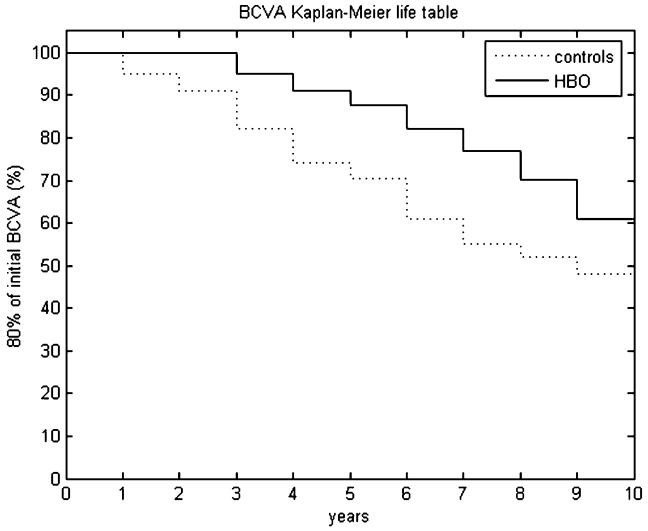

Fig. 1 Kaplan-Meier life-table with the evaluation of the log-rank test for the two groups

same percentage of residual visual acuity was maintained in 40% of group 1 (X^2=3.22; p<0.05). Mean visual acuity was statistically different between the two groups after both 5 (p=0,008) and 10 years (p=0.026).

Considering visual field analysis with Goldmann perimetry, we obtained the following data: target I 4 patients with a visual field nasal extension (10° of eccentricity) were, respectively, 42% of HBO group and 68.4% of control group at the beginning of the study; visual field did not change in 31.6% of the HBO group and 10.5% of the control group at 10 years follow-up; target III 4 patients with a visual field nasal extension (10° of eccentricity) were, respectively, 15.8% of the HBO group and 36.8% of the control group at the beginning of the study; visual field did not change in 68.4% of the HBO group and 42.1% of the control group at 10 years follow-up. These data were statistically significant (p=0.034).

Considering conventional perimetry by HFA and, in particular, the evaluation of the whole mean defect, 68.4% of HBO patients preserved 80% of residual mean sensitivity compared to 42.1% of the control group patients at 5 years follow-up; 53% of HBO patients showed 80% of residual mean sensitivity compared to 23.5% of the control group patients, with a statistically significant result at 10 years of follow-up (X^2=4.72; p<0.035) as shown in Fig. 2.

As can be seen in Fig. 3, ERG b-wave mean amplitudes resulted in the HBO group as follows: at baseline 4.68±3.81 μV, after 1 year 8.46±5.71 μV, at 2 years 10.7±7.6 μV; at 3 years 14.94±11.7 μV, at 5 years 18.37±10.3 μV, and at 10 years 17.26±8.1 μV. In the control group ERG b-wave mean values were as follows: at baseline 4.92±3.05 μV, at 1 year 5.04±3.07 μV, at 2 years 3.46±2.77 μV; at 3 years 2.97±3.61 μV; at 5 years 8.54±2.6 μV, and at 10 years 7.26±

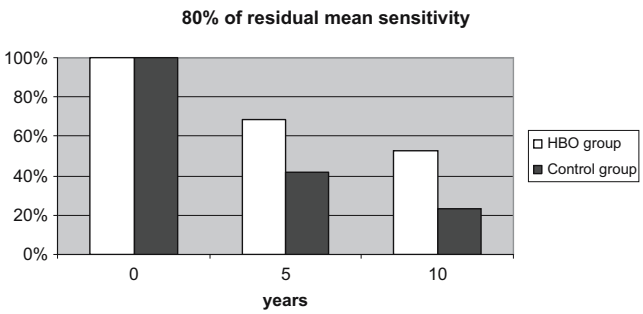

Fig. 2 Group comparison of 80% initial visual acuity retention

2.1 μV. ERG b-wave amplitudes registered during the first 3 years showed a highly significant (p<0.001) increase in patients treated with HBO, and a slightly significant (p<0.03) worsening in ERG b-wave amplitudes was evidenced in the control group. The sudden increase in the ERG b-wave values obtained at 5 and 10 years follow-up is due to the fact that in 2000 we changed our department ERG recording device resulting in a generalized increase of ERG values (i.e. noise level decreased from 5 μV in 1991 to 0.005 μV with today's ERG machines). Despite this, the results at 10 years follow-up highlight a statistically significant (X^2=4.53; p=0.013) improved performance in RP patients treated with HBO.

Discussion

Several studies revealed that retinal photoreceptor cells in normal conditions have a high oxidative metabolism and are strictly conditioned by metabolic speed and, consequently, by oxygen partial pressure in peripheral tissues [13]. In the presence of abnormal proteins, or phototransduction alterations, which may provoke photoreceptor retinal damage, more energetic support is needed to maintain a minimal visual function [14], as considered by Berson [3] with vitamin A treatment in RP patients.

In vivo studies by Stone et al. demonstrated that high levels of oxygen might partially rescue retinal photoreceptors in Royal College of Surgeons (RCS) rats, and

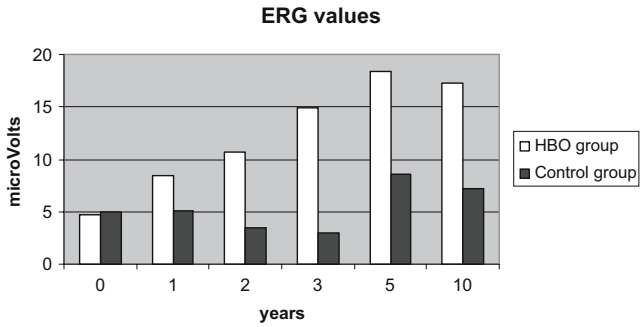

Fig. 3 ERG values

lower oxygen levels cause retinal damage in normal rat retina [15]. The same study also demonstrated that transient hyper-oxygen availability may slow retinal photoreceptors apoptosis, causing an increase of ERG max amplitude that may last for several months.

Moreover, studies demonstrated that patients affected by obstructive chronic lung disease with low PO2 levels present markedly altered ERG b-wave amplitude and latency [16].

RP patients show reduced retinal metabolism at an early stage of the disease, causing a heterogeneous group of symptoms characterized by night blindness, progressive constriction of the visual field caused by gradual degeneration of photoreceptor cells which proceeds from the periphery to the central region, and pigmented fundus abnormalities.

Variability of clinical expression [17] exists among patients with the same DNA mutations suggesting that other factors such as auto immunological disorders (auto antibodies against retinal antigens) [18] or alteration of choroidal and retinal vessels leading to a further metabolic defect of visual photoreceptors may influence the natural history of the disease.

However, loss of ocular blood flow decreases the oxygen tension in the choroid and retina, especially in the region immediately adjacent to the segment of the photoreceptors which are densely packed with mitochondria [19, 20]. An increase of oxygen availability, as induced by HBO, could complete metabolic requests, and may implement photoreceptor metabolic request, lower damage progression in visual function, both in VA and in visual field, increase significantly ERG amplitude, and positively influence the natural course of RP as demonstrated in this study.

HBO in retinal and optic disk vascular disease was also used in cases of occlusion of central vein resulting in an improvement of macular edema with marked changes in visual acuity and amount of leakage in more than 80% of patients [21] and in cases of Susac syndrome (recurrent branch retinal artery occlusion) with full recovery of visual acuity and visual field extension [22].

A recent paper reported a marked improvement of visual performances regarding visual acuity and visual field after HBO in two patients with nonarteritic anterior optic neuropathy nonresponsive to steroid therapy lasting 3–5 months after the event [23].

Concerning the effect of HBO in RP patients, there are few reports in the literature. Verin [24] found an improvement of visual acuity in three RP patients treated with HBO exposure. Skogstad [25] reported a lateral vision improvement after cessation of the treatment in one patient, and positive results were reported by Chachia [26] for one RP patient with cystoid macular edema.

HBO action may play a role in different sites where metabolic supply is consistently needed, determining increase in metabolic activity, mainly due to higher ATP availability [27]. To explain HBO positive effects we have to consider that different inherited errors in protein structure can cause malfunction in cellular metabolism at several steps, consequently leading to retinal cell apoptosis and pigment migration. In this context HBO contributes to supply an oversized energetic amount that has a relevant efficacy in photoreceptor recovery. The main possible points of HBO action are better efficiency in rhodopsin inactivation, better equilibrium in rhodopsin cascade, improved transduction activation caused by high levels of energy available with HBO, guanylate cyclase improved efficiency and availability, and better efficiency in rhodopsin conformational changes due to a higher amount of ATP molecules.

The main bias of the study is that, with this treatment, it is not possible to realize a true double-blind study because HBO requires active cooperation by the patient, and even if we did not add oxygen during the therapy, the amount that reaches the retina is higher than normal, and this may alter the results.

However, it is possible to conclude that in our long term study HBO delivery determines a long lasting effect in RP patients, contributing to the stabilization of their clinical conditions.

Furthermore, HBO therapy is a simple, very low-cost and little-time-consuming therapy which does not have important effects on the quality of life of these patients and has a very low rate of complications.

Even if our study demonstrates a consistent change of clinical conditions, this is only an increase in functional responses and it could not imply a consistent change in disease progression; unfortunately, this study is not the final cut, but represents an attempt at the possibility of developing an antiapoptotic therapy for tapetoretinal degenerations waiting for a definitive cure.

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