POSSIBILITIES OF HYPERBARIC OXYGEN THERAPY USAGE IN COMPREHENSIVE TREATMENT OF SELECTED HEARING DISEASES AND DISORDERS

Minireview

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Abstract
Hearing disorders in congenital or progressive forms in childhood as well as in elderly period of life are very important factors, lowering patient´s quality of life and increasing of healthcare costs. Hyperbaric oxygen therapy could be very effective tool in the comprehensive healthcare in patients. In our minireview are described baseline premises for the exploitation of oxygen facilities at higher pressure for healing of auditory system.

Key words: hearing loss, hyperbaric oxygen therapy, quality of life.

1 Introduction

Changes in sensory sensitivity and acuity, and in cognitive processing, are among the most robust findings lowering human´s well-being. Such declines will become more common as the world's population shifts towards a greater number of older adults [1]. Both age-related hearing loss and cognitive decline are associated with communication difficulties, isolation, decreased quality of life, and depression [2-6]. Recently, Lin et al. [7] have suggested that hearing loss may play a causal role in precipitating cognitive decline and the relationship between hearing loss and cognitive decline has attracted increased attention in recent months [2]. The growing increase in age-related hearing loss, with its dramatic reduction in quality of life and significant increase in health care costs, is a catalyst to develop new therapeutic strategies to prevent or reduce this aging-associated condition [8].

2 Selected hearing diseases and disorders

Despite the fact that age-related hearing loss affects more than one-third of the world population over 60 years-old, rising to more than two-third of those in their 70's [8-12], currently there is no available medical treatment for this age-related sensory dysfunction. This has led to an important humanitarian cost in terms of isolation, frustration, depression, cognitive decline and decrease in quality of life, along with an enormous and growing economic burden in health care costs [13-17]. In this regard, there is extensive evidence that excessive free radical formation along with diminished cochlear blood flow are essential factors involved in mechanisms of other stress-related hearing loss, such as that associated with noise or ototoxic drug exposure. The emerging view is that both play key roles in age-related hearing loss pathogenesis [8].

Sudden sensorineural hearing loss (SSNHL) is defined as 30dB or more of sensorineural hearing loss over at least three consecutive frequencies within 3 days [18-22]. In total, 85–90% of cases are idiopathic at presentation [23]. Viral infections, vascular compromise, autoimmunity, and intralabyrinthine membrane rupture are considered as the main potential causes of idiopathic SSNHL (ISSNHL) [18, 24-26]. The degree of hearing loss, time period from the onset of hearing loss and beginning of treatment, audiometric configuration,

comorbidities (hypertension, diabetes), and presence of vestibular symptoms and tinnitus may influence the course of ISSNHL [24, 27].

Tinnitus, the phantom perception of sound, is physiologically characterized by an increase in spontaneous neural activity in the central auditory system. However, as tinnitus is often associated with hearing impairment, it is unclear how a decrease of afferent drive can result in central hyperactivity [28]. Associative risks for tinnitus include intense noise exposure, ototoxic insults, head and neck injuries, and age-related hearing impairment [28-32]. Peripheral trauma causes partial deafferentation of the auditory nerve fibers, which reduces afferent drive to its central target, the cochlear nucleus. However, in experimental animal models, noise-trauma paradoxically induces elevated spontaneous activity in ventral and dorsal cochlear nuclei [28].

3 Genetical background

A wide spectrum of hearing loss or sensory sensitivity and acuity has been revealed in the recent years. Connexin 26 (Cx26, *GJB2*) mutations belongs to the most recently investigated causes of non-syndromic hearing loss in children [33]. This gene belongs to the connexin gene family comprising more than 20 isoforms, which is responsible for coding of specific gap junctional channels in cells. This connexin gap junctions play an important role in hearing. Previous studies had shown that connexin mutations are responsible for more than half of hereditary hearing loss [34-38]. Connexin 26 mutations can be autosomal dominant, autosomal recessive and also linked on X-chromosome. Nowadays there are known more than 100 *GJB2* mutations [39], which can variate in clinic from moderate to profound hearing loss. Very interesting is the fact, that pathological changes cannot be always congenital and there are also known cases of later onset and progression starting in childhood [40, 41].

Structural genes, however, are not the only cause of hearing disorders. Another important source of hearing problems has metabolic origin. Gene for phosphoribosylpyrophospohate synthetase 1 (*PRPS1*) is an example of the mentioned impact of metabolic pathways on the auditory system. *PRPS1* gene is localized on the longer arm of the X-chromosome (Xq22.3) and codes enzyme PRS-I that catalyses the first step of *de novo* synthesis of purine and pyrimidine nucleotides [42-44]. *PRPS1* gene has been found to be expressed in cochlea, vestibular organs and utricle with the *mir-376* MicroRNA regulation of the transcript level [45-47]. There are variable palette of clinical manifestation of PRS-I deficiency beginning with moderate hearing deficiency (X-linked Nonsyndromic Sensorineural Hearing Deafness, DFNX-2) and continuing with extremely rare profounder hearing loss as a part of complex palette of symptoms (Charcot-Marie-Tooth Disease, CMTX5). The most severe X-linked PRS-1 hypofunction syndrome is the Arts syndrome, which is characterized by profound bilateral sensorineural hearing loss accompanied with ataxia, intellectual disability and delayed motor development [43, 48-52]. All above mentioned disorders has common cause in the form of mutations modulating the enzyme conformation and activity.

4 Proposed therapy strategies

An excess of reactive oxygen species (ROS) in the cochlear sensory epithelium, spiral ganglion neurons and cells of the stria vascularis may have a relevant role in the development of age-related hearing loss. Of importance, excessive ROS build up is clearly the key factor in the pathogenesis of other stress-induced otological conditions that also result in reduced auditory function, such as noise and drug induced hearing loss. These findings provide the rationale to support the hypothesis that therapeutic strategies targeting ROS overproduction may be potentially useful not only for ameliorating noise and drug induced hearing loss but also to improve age-related hearing loss. Although there is still controversy about the benefits of using free radical scavengers for the treatment of ROS induced cochlear damage, most studies seem to agree that antioxidants reduce structural and functional stress-induced pathology in the

inner ear in experimental animals. For instance, mannitol, N-acetylcysteine, acetyl-L-carnitine, sallicylates combined with N-acetylcysteine, trolox or vitamins A, C, and E attenuate inner ear damage following noise-induce hearing loss. Similarly, D-methionine, N-acetylcysteine or a combination of vitamins A, C, and E also have been shown to protect the cochlea after drug ototoxicity [8].

In addition to free radical generation in the cochlea, reduction in cochlear blood flow and vascular conductance during aging is another main contributor to cochlear damage. In the circulating blood volume the reductions that may reach up to 20% in the cerebral flow [53]. Despite the strong autoregulation of cochlear blood flow that occurs under normal conditions, the cochlea is no exception to this rule, as a significant decrease in blood flow regulation as well as in blood supply to the cochlea occurs during aging, particularly in the stria vascularis, in a number of animal models and man. Age-related alterations in the microvasculature of the stria vascularis, have been found to correlate with the increase in auditory thresholds observed in presbyacusis, a condition known as strial or ‘‘metabolic’’ presbyacusis, as well as in noise and drug induced hearing loss. The stria vascularis is pivotal in maintaining the endocochlear potential (EP) as alterations in its structure and function induce a progressive decrease in the EP, finally affecting the cochlear amplification of acoustic signals. Thus, diminished cochlear blood flow may contribute to damage to the stria vascularis and altered hair cell function (with or without cell death) and to aging-related increases in auditory thresholds. It is worth noting that recent evidence shows that there is a significant involvement of strial presbyacusis in the genesis of the age-related hearing loss, leading to the suggestion that alterations in the stria vascularis could be the major cause of hearing loss during aging. In line with these observations, pharmacological up-regulation of cochlear blood flow could provide a vital treatment for age-related hearing loss [8].

Treatment protocols for ISSNHL aim to decrease the inflammatory state of the inner ear and to increase the blood supply and oxygenation [18, 54]. Steroids, vasodilators, plasma expanders, and antiviral and diuretic agents are preferred for these purposes in different combinations [56]. Low-molecular-weight heparin and hyperbaric oxygen therapies have also been reported to have some treatment advantages [27, 54].

Hyperbaric oxygen therapy (HBOT) is a therapeutic approach where the patient is exposed to 100% oxygen at pressures higher than ambient (1 ATA). This leads to an increased blood oxygen level, which than can penetrate to ischemic areas more deeply than under normobaric conditions [56, 57]. Normally 97% of the oxygen transported from the lungs to the tissues is carried in chemical combination with hemoglobin or red blood cells, and the remaining 3% in a dissolved state in plasma. Under hyperbaric conditions, it is possible to dissolve sufficient oxygen, i.e., 6 vol% in plasma, to meet the usual requirements of the body [58, 59]. HBOT is a standard therapy for decompression sickness, gas embolism and CO poisoning [60, 61]. HBOT is also effective for gas gangrene, anaerobic infection, diabetic foot, Burger’s disease and other oxygen-deficient conditions [62, 63]. In addition, HBOT has been proved effective in the healing of chronic wound, such as radiation-induced soft tissue necrosis [64-67]. Meanwhile, many studies reported the therapeutic or preventive effect of HBOT in various kinds of inflammatory or immune-mediated diseases, such as systemic lupus erythematosus [68, 69], atherosclerosis [70], collagen-induced arthritis [71], Crohn’s disease [72], ulcerative colitis [73, 74] and atopic dermatitis [75], although these diseases are not included in the current indication of HBOT [76, 77].

Yang et al. [78] compared in their study the efficacy of intratympanic steroid injection (ITS), hyperbaric oxygen (HBO), and combination therapy as salvage treatment in patients with sudden sensorineural hearing loss (SSNHL) after failure of systemic therapy. One hundred three refractory SSNHL patients are enrolled. Among them, 35 received ITS alone, 22 received HBO alone, 19 received combined ITS and HBO, and 27 received no salvage

therapies. Hearing outcomes were determined by hearing gains in pure-tone average, recovery rate, and word recognition score measured by audiometry before and after salvage therapies. Their results indicated significant larger hearing gains in pure-tone average found in the ITS, HBO, and combined groups than the control group. The combination of ITS and HBO resulted in a significantly larger word recognition score improvement than the control group ($p = 0.035$) and larger hearing gains than the ITS and HBO groups especially in lower frequencies (250 Hz).

HBOT can lead to significant improvement of pure tone hearing thresholds in patients with SSHL who failed primary corticosteroid treatment and are within 4 weeks of the onset of deafness [79].

Kaya et al. [26] evaluated the effectiveness of vitamins A, C, and E, with selenium, in the treatment of ISSNHL. In a prospective, controlled study over a 32-month period, patients were treated with either standard ISSNHL treatment regimen plus vitamins A, C, and E and selenium or with only standard ISSNHL treatment regimen. Treatment with vitamins A, C, and E and selenium was effective in ISSNHL patients undergoing treatment with methylprednisolone, dextran, trimetazidine dihydrochloride, and HBOT, and might be more effective when the initial hearing level is below 46 dB.

Porubsky et al. [80] analyzed the effectiveness of HBOT in the context of accompanying factors. They randomized 360 patients suffering from tinnitus into 2 HBO treatment protocols (group A: 2.2 bar for 60 min bottom time and group B: 2.5 bar for 60 min bottom time once a day for 15 days). All patients were asked to fill in a questionnaire (social and medical history, tinnitus characteristics, pre-HBO duration of tinnitus, prior therapy, pretreatment expectation, accompanying symptoms). A subjective assessment of the therapeutic effect was obtained. Twelve patients (3.3%) experienced complete remission of tinnitus, in 122 (33.9) the intensity lessened, and 44 (12.2%) had a subjectively agreeable change of noise characteristics. No change was found in 157 cases (43.6%) and 25 (6.9%) experienced deterioration. There was no statistically significant difference between groups A and B ($p > 0.05$). Out of 68 patients with a positive expectation of HBO effects, 60.3% stated that the tinnitus had improved whereas only 47.2 and 19%, respectively, out of patients who underwent therapy with an indifferent ($n = 271$) or negative expectation ($n = 21$) reported an improvement. The influence of subjective expectation on the outcome was statistically significant ($p < 0.05$). Based on their results, the therapeutic effects of HBO on subjective tinnitus may be substantially influenced by psychological mechanisms.

Furthermore, Lamm et al. [81] evaluated more than 50 studies with a total of 4 109 patients suffering from idiopathic sudden hearing loss, acoustic trauma or noise-induced hearing loss and/or tinnitus, HBOT was administered as a secondary therapy, i.e. following unsuccessful conventional therapy. If the onset of affliction was more than 2 weeks but no longer than 6 weeks, one half of the cases showed a marked hearing gain (in at least 3 frequencies of more than 20 dB), one-third showed a moderate improvement (10-20 dB) and 13% showed no hearing improvement at all. 4% no longer experienced tinnitus, 81.3% observed an intensity decrease and 1.2% an intensity increase of their tinnitus condition. 13.5% remained unchanged. If HBOT was administered at a later stage, but still within 3 months following onset of affliction, 13% showed a definite improvement in hearing, 25% a moderate improvement and 62% no improvement at all. 7% no longer suffered from tinnitus, 44% reported an intensity decrease, a similar percentage noticed no change and 5% a temporary deterioration of their tinnitus condition. If the onset of affliction was longer than 3 months up to several years, no hearing improvement can be expected in the majority of patients; however, one third of the cases reported an intensity decrease of tinnitus, 60-62% reported no change and 4-7% noticed a temporary intensity increase. In conclusion, it may be deduced that HBOT is recommended

and warranted in those patients with idiopathic sudden deafness, acoustic trauma or noise-induced hearing loss within 3 months after onset of disorder.

6 Conclusion

Hyperbaric oxygen therapy is the unique method of increasing concentration of oxygen in the inner ear fluids thus facilitates the regeneration process. In combination with therapeutic targeting of excessive free radical formation and cochlear blood flow regulation may be therefore a useful strategy to improving auditory function of selected hearing diseases and disorders.

Further comprehensive clinical trials are needed in formation of standardized therapeutical procedures with defined sequences of treatment interventions and known estimated range of laboratory determinated parameters. The task of our project is to fill-out this area of knowledge with the emphasis on the needs of the local population.

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