Critical Review:
Can the use of folate or Vitamin B_{12} affect the process of age-related hearing loss?

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This review examined the published evidence for the existence of a relationship between folate and/or vitamin B_{12} status and age-related hearing loss, otherwise known as presbycusis. Based on vascular research, it was hypothesized that a decline in folate or vitamin B_{12} levels could detrimentally affect the highly-vascularized cochlea, especially the stria vascularis, thus resulting in increased hearing threshold levels. Some of the studies examined herein used a correlational design and non-parametric statistical analysis and others used randomized controlled clinical trials with t-testing or ANCOVA—all with human subjects. The results were mixed, with some supporting a relationship and others not.

Introduction

Old age brings with it many infirmities, one of which is presbycusis. Presbycusis is a sensorineural hearing loss caused by the aging process alone (that is to say, not middle ear dysfunction or disease, or a medical or genetic condition). Based on work by Gates et al. (1999) and Willot (1996), Berner et al. (2000) concluded that presbycusis has both genetic components and environmental components "such as noise, oto-toxic drugs and infections" (p. 633), while Darrat et al (2007) added "'random' alterations in the structure and function of macromolecules, cells and organ systems" (p. 358). Darrat et al (2007) continued that, according to their own research, "oxidative stress, resulting in increased mitochondrial DNA mutations and a concomitant reduction in mitochondrial function [is one of the factors in the aging process]. These changes ultimately lead to cellular and subcellular dysfunction, which [probably results in a] significant decrease in auditory sensitivity. The generation of [reactive oxygen species] is partly responsible for the reduction in the mitochondrial membrane potential and the loss of cochlear hair cells, with an attendant increase in the auditory threshold." (p. 359)

Overall bodily health can also affect the auditory system. In particular, poor vascular health can affect the cochlea since it is heavily vascularized, thereby affecting hearing (Houston et al, 1999, Durga et al., 2006). Ubbink et al. (1993) and Welch and Loscalzo (1998) pointed to links between low folate or B vitamin levels and elevated homocysteine as being risk factors for vascular disease. Researchers have hypothesized that elevated homocysteine levels, which "have been associated with…changes in microvessel flow mechanics…may be linked to the changes in microvessel permeability, cochlear blood flow and stria vascularis atrophy" (Durga et al, 2006, p. 483) thus resulting in hearing loss.

There are many factors that affect a person's blood concentration of folate and vitamin B_{12}. Diet (Hughes, 1989) has been shown to affect folate and B_{12} levels. Medical conditions associated with the aging process such as atrophic gastritis (Krasinski et al., 1986) have been shown to cause malabsorption of folate and vitamin B_{12}. Following other researchers[1] Houston et al. (1999) stated that because folate and B_{12} have "roles…in cellular metabolism, the nervous system, and vascular function" (p. 564) this malabsorption and resulting decline in folate and B_{12} levels could be associated with the progression of presbycusis.

In addition, Houston et al (1999) hypothesized that B_{12} deficiency may impair myelination of neurons in the cochlear nerve, thus affecting hearing.

Objective

The objective of this paper is to critically review the literature in order to discover whether a positive relationship exists between folic acid or vitamin B_{12} level and presbycusis.

Methods

<u>Search Strategy</u>
Online search engines such as CINAHL, Scopus and PubMed as well as Google Scholar were used to look for journal articles. The initial search was (antioxidants AND ("hearing loss" OR presbycusis) AND NOT

[1] Shemesh et al (1993), Brant et al (1996), Gates et al (1993) and Herbert et al (1994)

noise). After the initial search yielded a great many articles, the search was narrowed to just ((“folic acid” OR “Vitamin B12”) AND “age related hearing loss”).

Selection Criteria

The narrowed search criteria yielded both animal and human studies. Because the focus of this review was to endeavour to see whether there were benefits to humans, this paper concentrated on the human studies. This concentration resulted in the final 5 studies: two of which were done by members of one research team (Houston et al, 1999 and Park et al, 2007) and another two which were done by another research team (Durga et al, 2006 and 2007) as well as a study by Berner et al (2000).

Data Collection

Three papers (Houston et al (1999), Berner et al (2000) and Durga et al (2006)) utilized correlational studies, one, Park et al (2007), comprised both a correlational study and a randomized controlled trial, and the last (Durga et al, (2007)) employed a fully-randomized controlled trial.

Results

The papers cited here all reported that vascular health is associated with folate/B_{12} status and its effect on cochlear health. One paper (Durga et al, 2006) also examined a genetic mutation related to folate concentrations in the blood and resultant elevated homocysteine levels (which in turn are associated with low folate and B_{12} levels).

The studies examined herein attempted to control for hearing loss due to other factors than presbycusis, by excluding subjects with conditions such as noise-induced hearing loss, diabetes, middle ear dysfunction, genetic history of hearing loss and unilateral hearing loss. Otoscopy was conducted to reveal any disorders of the ear canal and, except for one study (Park et al, 2007) audiometric exams were conducted in a hearing clinic. Baseline audiometric testing was conducted on all subjects and in the randomized controlled trials, post-treatment testing was also conducted. Air and bone conduction thresholds were determined on the octaves for both ears. Blood was drawn for analysis after fasting for most studies reviewed.

The Correlational Studies

Houston et al’s 1999 study appears to be the first in the literature to examine a possible relation between folate or B_{12} status in humans and age-related change in hearing thresholds. Subjects were 55 white, young elderly (aged between 60 and 71 years, mean 65) community-living women. Average daily intake of folate and B_{12} was calculated after obtaining a total of three days of dietary records. Supplementation was taken into consideration and subjects’ total folate and B_{12} intake included both dietary intake and that of supplements. Subjects’ blood was collected for analysis after an overnight fast and serum B_{12}, red cell folate and serum folate levels were ascertained for each subject. Hearing level was determined by the pure-tone air conduction average of 0.5, 1, 2 and 4 kHz of the subjects’ better ears. Subjects were then divided into ‘normal hearing’ and ‘impaired hearing’ groups, the cut-off for which was a PTA of <20 dB HL. Houston et al used logistic regression analyses to ascertain whether a relationship existed between their subjects’ hearing thresholds and their folate and B_{12} status. When controlled for age, a significant correlation was found between serum B_{12} and red cell folate levels and hearing thresholds. Intake was also significantly associated with hearing thresholds, although the association was stronger for folate than for B_{12} with 64% of hearing impaired subjects having a folate intake less than the recommended daily allowance compared to only 16% of the normally-hearing subjects and 27% vs. 14% respectively for B_{12}. Additionally, when subjects were sub-divided into groups of those taking supplements and those not, folate blood levels were the lowest in the hearing impaired women.

Berner et al (2000) attempted to replicate Houston et al’s results. Their sample was slightly larger (n=91), had a larger age range (67-88 yrs, median 78) and included 35 men. Subjects were selected from persons referred to the audiological department. Audiometric evaluation included speech reception thresholds in addition to pure-tone averages. Blood was drawn but whether or not subjects fasted was not noted. Folic acid, B_{12} and homocysteine levels were determined from analysis of the blood samples. Each subject’s audiometric and blood levels were analysed separately from the others and no hearing status groups were made; this makes any relationship more evident because hearing thresholds were matched to the subject’s own folate, B_{12}, and homocysteine status one-to-one. Once folate, B_{12}, and homocysteine were matched with hearing threshold, all matched blood level and hearing data were analysed as a set. A very weak but not significant positive correlation was found between homocysteine levels and hearing threshold. No relationship between folate or B_{12} and hearing threshold was found in their study of hearing impaired individuals.

Durga et al (2006) recruited 819 subjects from an existing study of folic acid and atherosclerosis. Of the 819 subjects (50-70 years old, mean 60), 590 were men and 301 post-menopausal women. Exclusion criteria for blood levels were low homocysteine and B_{12} levels, the use of B supplements or medications that affect folate levels. Pure-tone averages were divided into PTA-low (0.5, 1, 2 kHz) and PTA-high (4, 6, 8 kHz) for analysis. Blood was drawn after fasting and folate, B_{12} and homocysteine levels were ascertained. A questionnaire was given to the subjects concerning their food consumption and the results were used to estimate the past 3 months' folate intake. On analyzing the folate, B_{12} and homocysteine levels with relation to hearing thresholds, Durga et al found that folate and B_{12} (but not homocysteine) were significantly related to elevated PTA-high and PTA-low thresholds but their results were the opposite of their hypothesis in that high B vitamin levels were associated with elevated hearing thresholds.

Park et al (2006) recruited their 93 participants (range 58-92 years old, mean 75) from a nutritional program at a local senior's centre. They proposed that since B_{12} deficiency had been correlated with elevated hearing thresholds, tinnitus and auditory hallucinations, and elevated serum methylmalonic acid (MMA) was associated with B_{12} deficiency, a relationship between hearing thresholds and elevated MMA, as well as high total homocysteine and/or low serum B_{12}, was possible. Blood was drawn from the subjects without fasting. Tympanometry was conducted to assess middle ear functioning. Air-conduction thresholds were tested in a quiet area, rather than a sound booth, so PTA was modified to exclude 500 Hz. PTA was found to be significantly correlated with MMA levels. Subjects in the hearing impaired group had elevated MMA compared with those in the normal hearing group for their worse ear but not their better ear. However, serum total homocysteine was not found to be significantly different between normal and impaired hearing groups. It was hypothesized that serum MMA could be a particularly sensitive indicator of B_{12} status since it was the only measure of B_{12} that was correlated with hearing level.

The Randomized Controlled Trials

Park et al (2006) conducted a randomized, double-blinded design in addition to their correlational analysis. Subjects with normal blood levels of MMA were assigned to either receive a placebo, a supplement containing 25 μg/d of B_{12} or a supplement containing 100 μg/d of B_{12}. Subjects with elevated MMA received 1000 μg/d of B_{12} but no other treatment. Paired t-tests were used to analyze the baseline vs. post-treatment variables. After 3 months' supplementation, Park et al did not find any significant change in mean pure-tone average within groups. The authors estimated that their sample size gave 80% power to detect a 10% change with a $p = 0.05$. They concluded that the supplementation period had possibly been too short to find any results from supplementation. Alternatively, Park et al suggested that presbycusis was not reversible by B_{12} supplementation since other conditions such as cognitive deficits resulting from B_{12} deficiency are not reversible by supplementation.

Durga et al's 2007 study examined a similar group as their first. Exclusion criteria included extremely low or high homocysteine levels, the use of medicines that affect folate metabolism, or the use of B supplements. Their randomized clinical trial gave two different dosages of folate or a placebo to randomly-selected subjects (with the exception noted above of family members, who both received the same treatment). A statistically significant effect of supplementation was found after the 3-year trial with a remarkably good retention rate of subjects (only 16 did not return for final audiometric testing and 5 stopped participating before the trial finished) and cooperation rate (99% of the pills were consumed as required by those subjects who completed the study). The findings indicated that hearing thresholds rose in all groups but rose significantly less in the low frequencies (but not the high frequencies) of those in the treatment group. Unfortunately for the purposes of this paper, the high frequencies are those affected the most by age-related hearing loss.

Critique

Houston et al (1999) used only white females, therefore generalizability is limited to that group. Durga et al (2006 and 2007) looked at 819 people drawn from an already-established study group which looked at vascular health and a certain genotype. Immediately, this limits the generalizability of their results to the population at large. Another such limitation is the fact that the study also took place in the Netherlands, a country which, at the time of the study, prohibited folate fortification of foods. This limits the generalizability of the sample only to those countries which also do not allow fortification of food with folate.

Recruitment for Houston et al's 1999 study was via ads in community newspapers and on bulletin boards resulting in a possible selection bias against those who do not read the above. Durga et al (2006 and 2007) used subjects drawn from the same database for both studies. Given that the number of subjects was identical, it is not indicated whether the same subjects were used for the second study or whether overlap of subjects for the second study was avoided in some way.

Marital status was not noted except in Durga et al (2007) who noted that some of their subjects had another member of the family (living with them) who was also involved in their study. Marital status, education and socioeconomic status is known to have an effect on nutritional levels. Future research studies should attempt to measure or control these factors in order to ascertain the effect of long-term nutritional intake and any potential effect on the study results. Reidiger and Moghadasian (2008) found links between higher socioeconomic status and education level, gender (being female), marital status (married vs. common-law/never married) and nutrition, specifically higher fruit and vegetable intake.

For comparison purposes, all the studies that included normal hearing subjects except Houston et al used a cut-off PTA of 25 dB HL to designate normal hearing. People with varying hearing losses were included in the reviewed studies; for example, subjects with a mean mild to severe sloping loss (Berner et al, 2000), mean normal to mild loss (Durga et al, 2006 & 2007) and a mean moderately-severe loss (impaired group) (Park et al, 2006) were tested. The difference in cut-off makes it challenging to compare Houston et al's grouped results to the others, especially since Houston et al's mean of 26.8 dB HL (SD 5.5, range 20-35) for their impaired group was just above the other studies' criterion for normality and their impaired hearing group was quite small to start with (n = 11).

In two of the studies, no blinding of subjects or research staff was noted. This could affect the subjects' food intake or reporting if they knew what the authors were measuring and could influence the form and tone of interviewers' questions. The studies relied on self-report rather than food diaries, which may have resulted in inaccurate estimates of intake.

However, in two studies, Durga et al (2006) and Park et al (2006), blinding was noted of some staff. In Durga et al's 2007 study, all subjects and staff were blinded—this ensures that the data are objectively obtained and analyzed.

Conclusions

The papers conflicted in their results; some found an effect of folate or B_{12} status on hearing thresholds and others did not. From the correlational studies, Houston et al statistically analysed their findings and found a significant correlation between folate status and hearing threshold in their impaired hearing group. Berner et al (2000) examined folate and B_{12} status vs. hearing thresholds in a correlational single-subject design study but did not find any relationship. Durga et al (2006) found, interestingly, that contrary to their and others' hypotheses, low levels of homocysteine and high levels of B vitamins were associated with elevated hearing thresholds. Park et al (2006) found that subjects with impaired hearing had significantly higher prevalence of B_{12} deficiency than those with normal hearing in their worst ear but not the best ear (correlational analysis).

From the randomized clinical trials, Park et al (2006) did not find a significant effect of 3 months' supplementation with vitamin B_{12}. Durga et al (2007) did find a statistically significant effect of 3 years' supplementation with folic acid. (Note: It is not clear whether the difference in supplementation (B_{12} vs. folate) would have any effect. Houston et al (1999) stated that due to both their small sample size and the high correlation between B_{12} and folate levels, they did not find a difference in the effect of B_{12} and folate in their results.) However, clinically, Durga et al's 2007 results would not have much effect since the improvement seen was just 0.7 dB and was only seen in the low frequencies (note that presbycusis affects predominantly the high frequencies).

Recommendations

Because of the mixed nature of the research results, a clinical recommendation to pursue treatment would be premature and unwise. More study is warranted with more control. A long-term study may shed some light on the effects of nutritional intake over an adult's lifetime. A comparison of subjects from those countries that have allowed folate fortification of food for a considerable period of time to those subjects from countries which prohibited it for the same period of time could provide more data for the analysis of this question.

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