Genetically-informed behavioral and cognitive interventions may improve management of tinnitus

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Abstract

Introduction: Psychological and behavioral interventions, such as Cognitive Behavioral Treatment (CBT) and Tinnitus Retraining Therapy (TRT), are commonly applied either alone or in combination for the management of tinnitus but selection of the intervention model remains arbitrary. Herein we evaluated the hypothesis that genetic markers may guide the choice of tinnitus treatment towards improved therapeutic outcomes.

Results: Patients with subjective idiopathic tinnitus were assigned to either a genetically-informed CBT or TRT intervention protocol based on the status of four single nucleotide polymorphisms (SNPs) of the dopamine and serotonin pathways, namely *COMT* rs4680, *HTR2A* rs7997012, *HTR2A* rs6311, and *TPH2* rs4570625, that have been associated with behavioral or cognitive responses (Group A), or to a conventional approach (Group B) in which the choice of treatment was not directed by genotypic data. Tinnitus Handicap Index (THI) scores of perceived tinnitus severity were recorded at the initial and at the fourth session of treatment using appropriate questionnaires. A statistically significant reduction in the THI scores was evident only in the genotype-guided group A ($t = 3.03$, $p = 0.01$).

Conclusion: Individualized incorporation of genetic information may improve the outcome of behavioral and cognitive interventions in tinnitus.

Introduction

Tinnitus is a commonly reported medical symptom of unknown etiology and genetic influences that is experienced by up to 15% of the general population. In severe cases, it may lead to serious adverse effects on health and everyday life, including anxiety, insomnia and depression [1].

The primary objective of tinnitus therapy entails the reduction of perceived intensity of tinnitus by addressing its emotional and cognitive impacts [2]. Among the management options, cognitive behavioral treatment (CBT) has shown an improvement in the quality of life scores when applied to idiopathic tinnitus [1] Behavioral interventions based on the neurophysiological model initially reported by Jastreboff and Hazel [3] such as relaxation, education and tinnitus retraining treatment (TRT) are useful alternatives or adjuvants to CBT [4].

Nonetheless, selection of the intervention model by the physician remains arbitrary. We hypothesized that, similar to other pathologies where therapies are guided by genetic information, genetic markers may also assist in the choice of tinnitus therapy. Herein, we have explored the efficacy of a personalized tinnitus management plan that is based on the status of four single nucleotide polymorphisms (SNPs) associated with behavioral or cognitive responses, namely *COMT* rs4680, *HTR2A* rs7997012, *HTR2A* rs6311, and *TPH2* rs4570625.

COMT (catechol-O-methyltransferase) has attracted significant attention as the enzyme that catalyzes the breakdown of dopamine. A G→A single nucleotide polymorphism (rs4680) at codon 158 of *COMT*

changes valine (Val) to methionine (Met), resulting in lower enzymatic activity and, thus, elevated levels of dopamine. The greater synaptic availability of dopamine in Met/Met carriers has been associated with increased sensitivity to painful stimuli and higher levels of anxiety and overall response to psychosocial stress relative to Val/Val carriers [5 6]. Additional SNPs that have been explored in cognitive interventions, mainly in the context of depression, involve the serotonin signaling system, in particular HTR2A rs7997012, HTR2A rs6311 and TPH2 rs4570625 [7].

Although COMT Val158Met has also been associated with increased susceptibility to the clinical manifestation of tinnitus [8], we reasoned that the four aforementioned polymorphisms may be of interest in tinnitus therapy due to their importance in psychological interventions rather than the pathobiology of the disease. In a small scale randomized control trial we demonstrate that genetically-guided selection of therapy provides significant advantage in improving perceived outcomes and quality of life of tinnitus patients.

Results

Development of a genetic algorithm for tinnitus management

Genetic information was utilized to draft a personalized patient management plan on the basis of the algorithm depicted in Fig. 1a.

COMT Met/Met carriers are more likely to develop depression after exposure to adverse events compared to Val/Val individuals [11]. In contrast, the Val/Val COMT polymorphisms are associated with better responses to brief structured psychological interventions in various chronic pathologies, compared with Met/Met carriers [12 13]. Thus, we reasoned that a TRT approach that is focusing on education and sound therapy rather than analytical cognitive and behavioral interventions will benefit Val/Val carriers, whereas COMT Met/Met tinnitus patients would benefit from CBT.

The decision on intervention protocol for heterozygous Val/Met COMT carriers was dependent on the genotypic results of the serotonin signaling-related gene polymorphisms *HTR2A* rs7997012, *HTR2A* rs6311 and *TPH2* rs4570625 that have been correlated with depression [14]. We reasoned that carriers of 2 or more G alleles in *HTR2A* (rs7997012 and rs6311) and at least one T allele in *TPH2* rs4570625 would, collectively, respond better to CBT (Fig. 1a).

Application of the genotype-based algorithm improves the outcome of tinnitus therapy

A total of 6 patients in each group received CBT, whereas 5 patients in group A and 4 patients in group B were offered TRT. One patient in Group A reported that she was not satisfied by the approach during the 3rd session. Consequently, further psychological support was suggested so that the patient could overcome avoidance behaviors and unhelpful thoughts, which were an obvious issue during the

examination and history taking. She was the only patient in Group A who did not complete the fourth session. In Group B, two patients did not complete all sessions and were excluded from further analyses.

Tinnitus Handicap Index (THI) scores were recorded at the initial and at the fourth session of treatment using appropriate questionnaires to quantify the impact of tinnitus on everyday function and its perceived severity. Initial and final results of the THI scores are presented in Fig. 1b for each patient and in Fig. 1c for each group. A statistically significant difference in the THI scores was found only in the genotype-guided group A ($t = 3.03$, $p = 0.01$; Table 2).

Table 2
Comparisons of initial and final THI scores for each intervention group

	CBT/TRT (No of patients)	Initial mean THI score (SD)	Final mean THI score (SD)	Paired t-test
Group A	6/5	52	43.3	$t = 3.03$, $p = 0.01$
Group B	6/4	53	50.4	$t = 1.14$, $p = 0.28$

Discussion

Although tinnitus is a relatively common medical condition, little is known about its pathophysiology. Aging and several environmental factors such as stress, smoking, sleep deprivation and poor working conditions have been implicated in the emergence of tinnitus [1 2]. A moderate genetic influence was inferred by a longitudinal twin study attributing approximately 40% of phenotypic variation in tinnitus to genetic factors [15]. Moreover, whereas a recent small-scale GWAS involving 167 tinnitus patients did not identify SNPs achieving the conventional threshold for genome-wide significance, the results pointed to the potential involvement of several cellular pathways associated with the most enriched SNPs, including oxidative stress, ER stress and, interestingly, serotonin receptor-mediated signaling [16]. Overall, the relative contributions of genetic *versus* environmental parameters to tinnitus remain unclear and hinder the development of specific therapies.

Currently, once treatable ontological pathology has been excluded, the management of tinnitus patients entails cognitive behavioral therapy (CBT), tinnitus retraining therapy (TRT) that includes counseling and sound-generator therapy, or their combination [4]. These management options aim to reduce the emotional and cognitive impacts of tinnitus that may include anxiety and depression. However, the choice of treatment by the physician remains arbitrary. As a significant proportion of patients do not respond to either one or both treatment forms or do not tolerate and complete them, it is both of scientific and clinical interest to identify biological markers for individualization of CBT and TRT intervention models [17].

Herein we explored the hypothesis that genetic markers related to the dopamine and serotonin pathways may assist in the choice of treatment. These pathways were selected for study as they impact behavioral

and/or cognitive responses and could thus be pertinent to current tinnitus management strategies. Indeed, anxiety is associated with both serotonin and tinnitus [18] and anti-depressants have been reported to confer beneficial effects on tinnitus [19]. Dopamine levels, influenced by polymorphisms of COMT (rs4680), modulate cognition, pain threshold and psychological distress, and COMT Met carriers with a more severe hearing loss perceive tinnitus louder in comparison to Val/Val patients [8].

These findings provided the foundation for the rational design of a genetic algorithm for the personalized management of tinnitus (Fig. 1a). Precision medicine does not only apply to pharmacological treatments, but also to psychological interventions for various chronic diseases [20]. Given that no prognostic factors, patient characteristics, and/or symptom characteristics for adults with subjective idiopathic tinnitus have been found to influence the final treatment outcomes, we reasoned that genetic information can be useful for the formulation of a more standardized cognitive/behavioral approach. Herein, we explored the status of four SNPs associated with behavioral or cognitive responses. In addition to their importance in behavioural interventions, these genetic variants are widely available in commercial genotyping tests. We confirmed the utility of the developed algorithm and demonstrated, in a pilot study, a statistically significant reduction in the perceived severity of tinnitus only in the genotype-guided group of tinnitus patients. Despite the fact that this reduction was of statistical importance, this is a rough estimation that needs to be interpreted with caution. A larger sample is required that will allow the interpretation of pre-interventional results in the analysis using for example a mixed model analysis of variance. In addition, larger samples will allow the estimation of the relative effect of each treatment (CBC/TRT) which is impossible with the data presented herein. Despite the limitations, this genetically-informed protocol is the first example of the potentially effective application of genetic information for the management of idiopathic tinnitus.

Conclusions

Individualized incorporation of genetic information associated with behavioral or cognitive responses improves the perceived severity of tinnitus, assessed by Tinnitus Handicap Index scores. This concept has broader implications in improving the outcomes of behavioral and cognitive interventions in tinnitus through the integration of genetic information, thereby addressing an unmet clinical need.

Materials And Methods

Patients and randomization

Twenty-four adult patients with bothersome bilateral non-pulsative tinnitus and hearing loss were divided into two groups (Table 1). Group A patients were offered a genetically based approach to tinnitus management that included a genetic test and at least three office based treatment sessions. A rationally-designed personalized management plan based on the genetic results is presented in Fig. 1a and is further described in the Results section above. In Group B, treatments were offered randomly taking care to offer CBT to equal number of patients as in Group A. The study was approved by the Ethics Committee

of the National & Kapodistrian University of Athens Medical School (No 208/2019). During the first visit, patients were offered a simple, few-minute tinnitus update and advice, relevant to their educational level and were suggested that an average of 4 sessions are required over a period of approx. 4 months for making tinnitus noise less or not bothersome.

Table 1
Randomized groups and treatments offered

	Group A (n = 12)	Group B (n = 12)	
Females (%)	6 (50%)	8 (66.6%)	$x^2 = 0.146$, p = 0.703
Age	51	56	t = 1.41, p = 0.09

Tinnitus Handicap Inventory (THI)

Upon a detailed history and an integrated ENT and audiological examination, the patients who consented in writing to participate in the study were asked to answer the THI, a questionnaire that quantifies the impact of tinnitus on everyday function. It is psychometrically robust and demonstrates adequate reliability and validity [9].

Genotyping

Mouth epithelial cells were collected using buccal swabs and DNA was extracted using the Pure-link Genomic DNA extraction mini kit from Invitrogen. Genotypes were analyzed on a Quant Studio 12X flex real-time thermo cycler (Applied Biosystems, Waltham, USA) using the following TaqMan SNP assays from Applied Biosystems: *COMT* rs4680 [ID assay: C_25746809_50], *HTR2A* rs7997012 [ID assay: C_1619749_10], *HTR2A* rs6311 [ID assay: C_8695278_10] and *TPH2* rs4570625 [ID assay: C_226207_10].

Cognitive Behavioral Treatment (CBT)

CBT is a psychologically informed treatment. Depending on individual patient needs, relevant areas of tinnitus education and management/self-management strategies, such as managing the emotional consequences of tinnitus, rapid relaxation, managing fear and avoidance behaviors and changing unhelpful thoughts and beliefs, were applied in accordance to a published manual [10].

Tinnitus Retraining Therapy (TRT)

TRT is based on the neurophysiological model focusing more on education and sound therapy than on analytical cognitive and behavioral interventions. A TRT program is usually included in a management scheme with hearing aids.

Statistics

Comparisons of THI scores and grades between groups were performed with the t-test. Statistical significance of the change of the THI scores was assessed with the paired t-test. Chi-squared test was utilized for nominal data.

Declarations

Ethics approval and consent to participate:

All procedures were in line with the principles of the Declaration of Helsinki. Written informed consent was acquired from all participants. The study was approved by the Ethics Committee of the National & Kapodistrian University of Athens Medical School (No 208/2019)

Consent for publication

All authors consented to publication

All patients consented to the publication of their data.

Availability of data and material

All data analyzed during this study are included in this published article. All related data is available upon reasonable request

Competing interests

Authors declare no conflicts of interest.

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Authors' contributions

KG performed the genetic analysis. IV and EP conducted patient treatment. KG, IV, MG, EP and AGE wrote the paper and approved the final version

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Figures

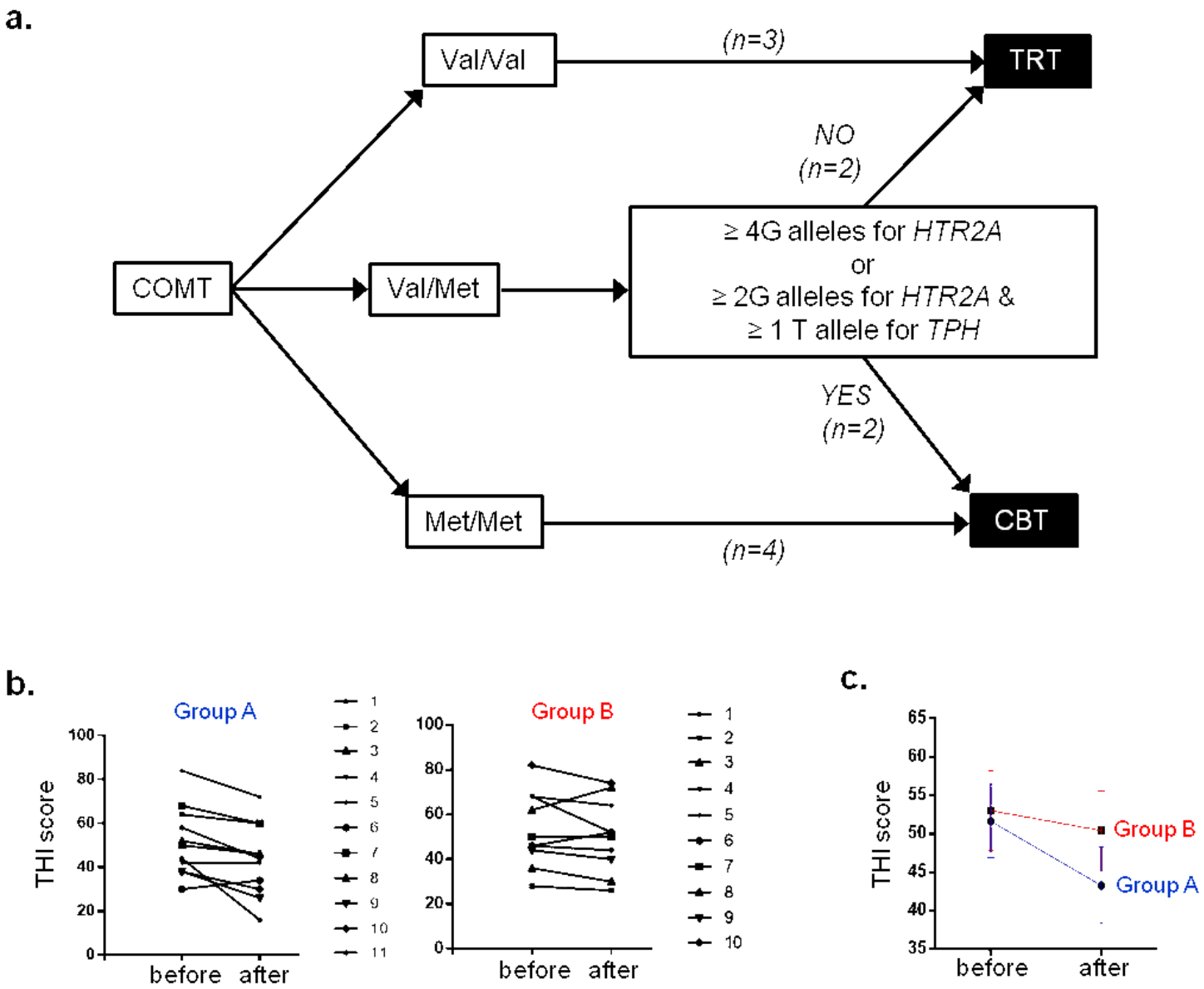

Figure 1

Genetically-informed behavioral and cognitive interventions improve management of tinnitus. (a) Schematic representation of the algorithm used to guide tinnitus therapy, TRT or CBT, in Group A patients (see Results section for details). (b & c) THI scores were recorded before and after conventional (Group B) or genetically-guided (Group A) interventions and depicted for each patient (b) or group (c).