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Coenzyme Q 10 and Cardiovascular Risk Factors in Idiopathic Sudden Sensorineural Hearing Loss Patients

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Objectives: We investigated the association of idiopathic sudden sensorineural hearing loss (ISSNHL) with coenzyme Q (CoQ) and cardiovascular risk factors.
Study Design: A prospective study.
Setting: Hospital center.
Patients: Thirty Italian patients with ISSNHL and 60 healthy Italian subjects.
Intervention: Diagnostic.
Main Outcome Measures: Evaluation of serum CoQ levels and cardiovascular risk factors (total cholesterol, low-density lipoprotein [LDL], homocysteine [HCY]). The results were compared with variance analysis and Student's *t* test. Univariate and multivariate analysis were used to evaluate the association between ISSNHL and CoQ, total cholesterol, LDL, and HCY levels.
Results: In our series, we found a significant association between ISSNHL and high total cholesterol ($p < 0.05$), high LDL ($p = 0.021$), and low CoQ ($p < 0.05$) levels. We did not find a significant association between ISSNHL and HCY levels. In the univariate analysis, low levels of CoQ, high levels of total cholesterol, and LDL were found to be significantly associated with ISSNHL. In the multivariate analysis, only high levels of total cholesterol and low levels of CoQ remained significantly associated with a high risk of sudden sensorineural hearing loss.
Conclusion: The studies regarding the role of cardiovascular risk factors in ISSNHL are not conclusive. This is the first report regarding the association of ISSNHL and low serum levels of the antioxidant CoQ. Further studies are needed to investigate the role of antioxidants, including CoQ, in ISSNHL. **Key Words:** Cholesterol—Coenzyme Q—Homocysteine—Low-density lipoproteins—Sudden sensorineural hearing loss.
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Sudden sensorineural hearing loss (SSNHL) is defined as a loss of at least 30 dB in 3 contiguous frequencies during a period of 3 days or fewer. Approximately 15,000 new cases of SSNHL occur annually worldwide, accounting for 1% of all cases of sensorineural hearing loss. A cause of SSNHL can be identified in only 10% to 15% of patients, whereas other cases are referred to as idiopathic. Idiopathic SSNHL (ISSNHL) is unlikely to result from a single cause, the main proposed etiologic mechanisms being membrane ruptures, infection, autoimmunity, or vascular disease.

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The hypothesis of vascular dysfunction has been favored because the onset of SSNHL is a sudden event, like myocardial infarction and cerebral stroke, but it has never been finally proven. In 1944, de Kleyn (1) reported vascular disorders as the underlying cause of SSNHL. In 1956, Hallberg (2) described the origin of SSNHL as a vascular accident in 50% of 178 patients. Schuknecht et al. (3) observed that alterations in the microcirculation of the cochlea may be a cause of SSNHL. In accordance with the theory of thromboembolism, abnormalities of rheologic factors in the blood of patients with idiopathic SSNHL have been investigated, and reduced erythrocyte filterability (4), high plasma viscosity, and high fibrinogen values have been reported to be associated with ISSNHL (5). At present, the few studies regarding genetic polymorphisms of congenital thrombophilic factors in SSNHL are not conclusive (6,7).

Concerning the association between SSNHL and cardiovascular risk factors, various authors have refuted the hypothesis of hyperlipidemia as a pathogenic factor in SSNHL (8,9), whereas others have suggested the possible role of hypercholesterolemia as a proatherogenic alteration (10).

According to the hypothesis that idiopathic SSNHL may be the result of pathologic activation of cellular stress pathways within the cochlea, the use of antioxidants has been recently encouraged. In fact, vitamin E, magnesium, and folate have been considered possible therapeutic targets in SSNHL (11,12). In an experimental model, it has been demonstrated that CoQ10 is effective in promoting recovery from acute sudden deafness damage to hypoxia (13), but the role of the antioxidant coenzyme Q (CoQ) in SSNHL has not yet been analyzed.

Coenzyme Q10 (2,3 dimethoxy-5 methyl-6-decaprenyl benzoquinone) is a fat-soluble, vitamin-like quinone commonly known as ubiquinone, CoQ, and vitamin Q10. Cenzyme Q is one of the two endogenous antioxidants that delay or prevent the oxidation of membrane-bound lipid peroxide free radicals (the other is vitamin E) (14). This role has important clinical implications because it is oxidation of lipid that contributes to the pathogenesis of atherosclerosis.

The objective of this study was to analyze if SSHL is associated with cardiovascular risk factors and low levels of CoQ by means of a prospective analysis of serum low-density lipoprotein (LDL), total cholesterol, homocysteine (HCY), and CoQ in patients with SSNHL. Data were compared with those for a control group of subjects with normal hearing.

MATERIALS AND METHODS

Patients and Controls

Subjects

All participants (patients and controls) were Caucasian. A total of 30 consecutive patients affected by SSNHL were included in the study; 17 women (mean age, 46 yr; range, 25–72 yr) and 13 men (mean age, 45 yr; range, 23–69 yr).

Exclusion criteria included a history of diabetes, stroke, cardiovascular disease, estrogen assumption, and vertigo. All patients had a negative history of familial deafness and metabolic diseases. All underwent a routine general physical examination. A total of 22 patients were nonsmokers, whereas 8 were regular smokers (>20 cigarettes per day). All patients consumed 2 servings or less of wine per day.

Pure-tone audiometry (frequencies, 125, 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz, International Organization for Standardization standard), speech discrimination test, impedance audiometry, auditory brainstem responses, electronystagmogram, computed dynamic posturography, and imaging (brain magnetic resonance, epi-aortic-vessel ultrasound) were performed in all patients. We used the following scale of hearing loss degree: mild, greater than 20 to 40 dB or less hearing loss; moderate, greater than 40 to 70 dB or less hearing loss; severe, greater than 70 to 90 dB or less hearing loss; and profound, greater than 90 dB hearing loss. From the date of the hospitalization, all patients were treated with a combined regimen of corticosteroids (1 mg/kg methylprednisolone daily) for 15 days, plasma expander (500 mL/d low molecular weight dextran) for 5 days, and 100 mg/d acetyl salicylic acid for 15 days.

Controls

Healthy Italian subjects without a history of hearing loss or autoimmune, metabolic, or circulatory diseases were included as matched controls: 26 men (mean age, 50 yr; range, 23–74 yr) and 34 women (mean age, 49 yr; range, 24–77 yr). Control subjects were recruited from clinic personnel and friends of patients. Patients and controls were unrelated. In addition, controls had been examined specifically for cardiovascular risk factors, metabolic, and autoimmune disorders at the time of recruitment. Chronic sensorineural hearing loss was excluded by pure-tone audiometry after routine ear-nose-throat examination. A total of 56 controls were nonsmokers, whereas 4 were regular smokers. All controls consumed 2 servings or fewer of wine per day.

Blood Tests

Blood was drawn by venipuncture at the moment of hospitalization and before the beginning of therapy. The following blood tests were performed: determination of CoQ, HCY, total cholesterol, and LDL-cholesterol levels; hemocytometric analysis, including platelet count; and determination of the prothrombine time, fibrinogen level, erythrocyte sedimentation rate, serum γ-globulin level and C-reactive protein level.

In our laboratory, normal levels of CoQ are defined as 0.60 to 1.0 mg/L, total HCY as 5.0 to 15 μM/mL, and total cholesterol and LDL cholesterol as 130 to 200 and less than 130 mg/dL, respectively.

Laboratory tests (determination of antiviral antibody titers) were also performed to exclude viral infections such as cytomegalovirus, herpes virus, Epstein-Barr virus, Coxsachie virus, hepatitis viruses B and C, and venereal disease.

Statistical Analysis

Variance analysis and Student's *t* test were used to compare the CoQ, HCY, total cholesterol, and LDL-cholesterol levels between patients and controls. Low CoQ status was defined as serum levels less than 0.60 mg/L; high HCY status as serum levels less than 15 μM; high total cholesterol and high LDL cholesterol status as serum levels less than 200 and 130 mg/dL, respectively.

The distribution of CoQ, HCY, total cholesterol, and LDL-cholesterol status according to cigarette smoking was analyzed using 2×2 contingency tables.

Univariate and multivariate analysis were used to evaluate the association between SSNHL and CoQ, total HCY, total cholesterol, and LDL cholesterol.

Odds ratios (ORs) are given with their 95% confidence interval (CI). Statistical significance was accepted at a level of $p < 0.05$. Statistical analyses were performed with the software package EPI INFO, version 3.3.2 (Atlanta, GA, USA).

RESULTS

Sudden sensorineural hearing loss was unilateral in 28 patients and bilateral in 2. Of the unilateral cases, SSHL was deep in 6 patients, severe in 8, moderate in 5, and mild in 9; bilateral cases presented moderate in 1 and

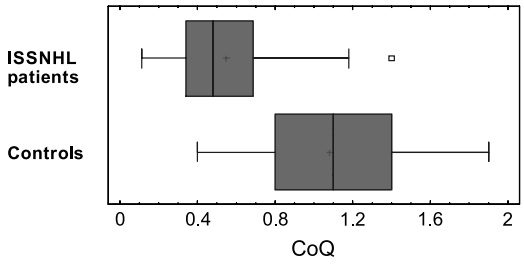

FIG. 1. Coenzyme Q serum levels in ISSNHL patients and controls.

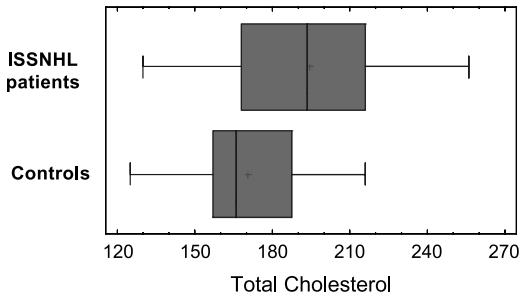

FIG. 3. Total cholesterol serum levels in ISSNHL patients and controls.

severe in another. No characteristic shape was detected: 16 patients had flat, 5 high-frequency, 2 U-shaped, and 7 low-frequency SSHL.

The diagrams in Figures 1–4 show the distribution of total cholesterol, LDL cholesterol, total HCY, CoQ serum levels in the patients, and control groups.

Total cholesterol levels ranged from 130 to 256 mg/dL (mean ± SD = 200 ± 38.95 mg/dL) in the SSNHL patients and from 125 to 303 mg/dL (mean ± SD = 175 ± 26.51 mg/dL) in the controls. Total cholesterol levels in the SSNHL patients were significantly higher in the SSNHL patients than in the controls (mean difference = 24.27; t = 3.483; 95% CI = 10.42–38.11; p = 0.000) (Table 1).

Low-density lipoprotein levels ranged from 76 to 159 mg/dL (mean ± SD = 128 ± 35.89 mg/dL) in the SSNHL patients and from 50 to 255 mg/dL (mean ± SD = 110.7 ± 31.34 mg/dL) in the controls. Low-density lipoprotein levels in the SSNHL patients were significantly higher than in the controls (mean difference = 17.35; t = 2.358; 95% CI = 2.726 – 31.97; p = 0.021) (Table 1).

Total HCY levels ranged from 4.5 to 14.1 μM (mean ± SD = 8.577 ± 2.503 μM) in the SSNHL patients and from 4.1 to 15.4 μM (mean ± SD = 9.223 ± 2.374 μM) in the controls. After variance analysis using Student's t test for serum HCY, the difference between the groups was not found to be significant according to our criteria (mean difference = −0.6467; t = −1.196; 95% CI = −1.721 to 0.4275; p = 0.235) (Table 1).

Coenzyme Q levels ranged from 0.11 to 1.1 mg/L (mean ± SD = 0.521 ± 0.26 mg/L) in the SSNHL population and from 0.4 to 1.9 mg/L (mean ± SD = 1.086 ± 0.38 mg/L) in the controls. Coenzyme Q levels in the SSNHL patients were significantly lower than in the controls (mean difference = 0.56; t = 7.27; 95% CI = −0.719 to −0.410; p = 0.000) (Table 1).

No statistically significant association between cigarette smoking and CoQ, HCY, total cholesterol, and LDL-cholesterol status was observed.

When all parameters were considered separately, low levels of CoQ, high levels of total cholesterol, and LDL were found to be significantly associated with SSNHL, whereas in the multivariate analysis, only high levels of total cholesterol (OR, 6.88; 95% CI= 2.267–20.890) and low levels of CoQ (OR, 18.00; 95% CI = 5.787–55.985) remained significantly associated with a high risk of SSNHL (Table 2).

DISCUSSION

We have demonstrated that low serum levels of CoQ, high total cholesterol, and LDL cholesterol levels were significantly associated with ISSNHL. However, only low serum CoQ levels and hypercholesterolemia resulted in independent risk factors for SSNHL in the multivariate analysis.

To our knowledge, this is the first report of an association between ISSNHL and CoQ serum levels.

In the otolaryngologic field, it has been reported that CoQ10 is effective in promoting recovery from acute sudden deafness. However, the pharmacokinetics of

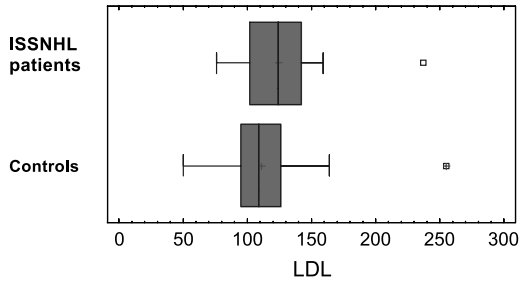

FIG. 2. Low-density lipoprotein serum levels in ISSNHL patients and controls.

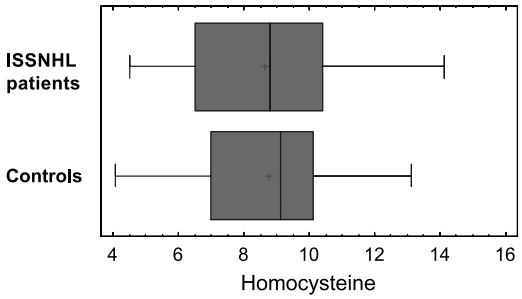

FIG. 4. Total HCY serum levels in ISSNHL patients and controls.

TABLE 1. *Distribution of the values of the variables CoQ, total cholesterol, LDL cholesterol, and HCY in patients and control groups*

Group	CoQ levels (mg/L)	95% CI	*p*	Total cholesterol (mg/dL)	95% CI	*p*	LDL levels (mg/dL)	95% CI	*p*	HCY (μM/L)	95% CI	*p*
Patients (n = 30)	0.52 ± 0.26	0.71–0.41	0.000	200 ± 38.95	10.42–38.11	0.000	128 ± 35.89	2.72–31.97	0.021	8.57 ± 2.50	1.72–0.42	0.4275
Controls (n = 60)	1.08 ± 0.38	—		175 ± 26.51	—		110 ± 31.34	—		9.22 ± 2.37	—	

p = Student's *t* test.

CoQ10 in the inner ear is not yet clarified. Recently, Angeli et al. (15) reported that CoQ10 may be helpful in delaying the progression of hearing loss in patients with the 7445A–>G mitochondrial mutation. In fact, they observed that CoQ10-treated patients did not show any additional deterioration of their SSNHL after 12 (familial case) and 13 months (sporadic case) to a patient who refused CoQ10 treatment and exhibited an 11-dB deterioration of his hearing thresholds.

Coenzyme Q10 (2,3 dimethoxy-5 methyl-6-decaprenyl benzoquinone) is a fat-soluble, vitamin-like quinone commonly known as ubiquinone, CoQ, and vitamin Q10. It is found in highest concentrations in tissues with high-energy turnover such as the heart, brain, liver, and kidney. Coenzyme Q10 has been indicated in the treatment of cardiac, neurologic, oncologic, and immunologic disorders (16–25).

Different studies demonstrated that CoQ has a key role in mitochondrial bioenergetics and is one of the two endogenous antioxidants within the LDL molecule (the other is vitamin E) (14). It is a part of a network of antioxidants that delay or prevent the oxidation of membrane-bound lipid peroxide free radicals. This role has important clinical implications because it is oxidation of lipid that contributes to the pathogenesis of atherosclerosis (26,27).

Concerning the association between ISSNHL and cardiovascular risk factors, various authors have refuted the hypothesis of hyperlipidemia as a pathogenic factor in ISSNHL (8,9). Conversely, we agree with the others who have suggested the possible role of hypercholesterolemia as a proatherogenic alteration (10). Hypercholesterolemia is a well-established risk factor for atherosclerosis and is associated with vascular occlusion of large arteries in coronary, cerebral, and peripheral regions. It is conceivable that a similar role in the impairment of cochlear perfusion, which is a vascular region, provided with a terminal capillary bed.

In our series, the results indicated that ISSNHL was significantly associated with high LDL cholesterol. In previous articles, it was reported that LDL and fibrinogen apheresis treatment in affected SHL patients improves the outcome of the disease. Low-density lipoprotein apheresis eliminates LDL particles from the circulation but also reduces the concentration of fibrinogen and other lipoprotein classes. The fast effect of LDL/fibrinogen apheresis was attributed to improved blood flow due to fibrinogen lowering and beneficial short-term effects of LDL reduction. Low-density lipoprotein reduction results in a more efficient release of nitric oxide, the mean mediator of blood vessel diameter. In the cochlea, production of nitric oxide by the cochlear vessels actively regulates regional blood flow. Release of nitric oxide is dependent on the integrity of endothelial function. Patients with raised concentrations of LDL cholesterol can have impaired endothelial function in coronary and peripheral arteries (28). Increased lipid peroxidation in the vessel wall and consecutive reduced synthesis of nitric oxide seems to be the underlying cause.

In our series, the significant association between low levels of serum CoQ, high levels of LDL cholesterol, and total cholesterol in a subset of ISSNHL patients permit us to suggest that these subjects can be treated

TABLE 2. *Univariate and multivariate analysis*

Univariate analysis (OR 95% CI)	*p*	Multivariate analysis	OR (95% CI)	*p*
Cholesterol (mg/dL)	6.88 (2.26–20.89)	0.0007	36.7 (3.25–414.52)	0.0036
<200		—	—	
>200	1*	—	—	
LDL (mg/dL)	3.25 (1.12–9.41)	0.0298	0.17 (0.01–1.98)	0.1589
<130		—	—	
>130	1*	—	—	
CoQ (mg/L)	18 (5.78–55.98)	0.0000	25.42 (6.90–93.60)	0.0000
>1		—	—	
<0.6	1*	—	—	

*Reference group.

with administration of CoQ to modulate oxidation of lipids and consequently favor endothelial function.

Research during the last decades has identified reactive oxygen species as the major factor mediating hearing loss, and Merchant et al. (29) hypothesized that ISSNHL may be the result of abnormal activation of cellular stress pathways. The role of antioxidants in reducing the inner ear damage and enhancing recovery in idiopathic SSNHL has been reported. Nevertheless, little information is available for the importance of the antioxidant status and, in particular, of the inner ear homeostasis and pathologic findings in humans.

At present, further studies are necessary to investigate if the reactive oxygen species system has a significant role in the pathogenesis of ISSNHL.

Concerning the suggested administration of CoQ in ISSNHL, no absolute contraindications are known for CoQ10. Adverse effects with CoQ10 are rare, and only mild gastrointestinal discomfort is reported in less than 1% of patients in clinical trials. Potential interactions with warfarin (Coumadin) and statins have been reported in case studies (30–32). Because of CoQ10's potential hypoglycemic and hypotensive effects, monitoring is advised, especially when using adjunctively with prescription medications.

Hyperhomocysteinemia has also been identified as a risk factor for cerebrovascular, peripheral, and coronary vascular disease. Elevated levels of plasma HCY can result from genetic disturbances in the transsulfuration or remethylation pathways for HCY metabolism. In previous studies, we failed to demonstrate an association between hyperhomocysteinemia and SSNHL, and neither the MTHFR C677T polymorphisms nor the levels of serum HCY were elevated in patients with ISSNHL compared with controls (7). In this series, high levels of HCY were not identified as a significant risk factor for SSNHL both in the univariate and in the multivariate analysis.

In agreement with previous observations (33), we did not find an association between CoQ status and smoking habits.

In conclusion, the studies regarding the role of cardiovascular risk factors in ISSNHL are not yet conclusive. Further experimental and clinical researches on a larger number of individuals should be directed toward a better understanding of the role of antioxidants, including CoQ, in ISSNHL.

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