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Lack of Association Between Inherited Thrombophilic Risk Factors and Idiopathic Sudden Sensorineural Hearing Loss in Italian Patients

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Objectives: We investigated the presence of congenital thrombophilic risk factors in a population of consecutive Italian patients affected by idiopathic sudden sensorineural hearing loss (SSNHL).

Methods: We investigated 48 patients with idiopathic SSNHL for the presence of congenital thrombophilic risk factors. The factor V Leiden G1691A, the prothrombin G20210A allele, and methylenetetrahydrofolate reductase (MTHFR) C677T genotypes were investigated. Allele frequencies and genotype distribution of all factors found in patients were compared to those of 48 healthy subjects of the same ethnic background by χ^2 and odds-ratio analysis. Odds ratios and 95% confidence intervals were calculated for allele and genotype frequencies of all thrombophilia variants. Statistical significance was accepted with a p value of less than .05. We also performed the following blood tests: hemacytometric analysis including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, erythrocyte sedimentation rate, C-reactive protein, protein S, protein C, antithrombin III, and activated protein C resistance.

Results: In our series, we did not find an association between SSNHL and abnormal levels of antithrombin III, protein C, protein S, D-dimer, or fibrinogen; activated protein C resistance; or factor V G1691A, prothrombin G20210A, or MTHFR C677T mutations.

Conclusions: At present, the few studies regarding genetic polymorphisms of congenital thrombophilic factors in SSNHL are not conclusive. According to our data, factor V G1691A, prothrombin G20210A, and MTHFR C677T variants should be not considered risk factors for SSNHL. Further large prospective studies are needed to provide currently lacking information and to improve our knowledge in the field before we recommend the determination of genetic polymorphism in SSNHL as routine practice.

Key Words: genetic polymorphism, inheritance, risk factor, sudden sensorineural hearing loss, thrombophilia.

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is defined as a loss of at least 30 dB in 3 contiguous frequencies over a period of 3 days or less. 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,[1] and other cases are referred to as idiopathic. Many treatment regimens have been proposed for idiopathic SSNHL, and even a "shotgun" therapy (vasodilators, plasma expanders, steroids, diuretics, carbogen, and histamine) has failed to improve the outcome as compared to spontaneous recovery.[2]

Idiopathic SSNHL is unlikely to result from a single cause; the main proposed etiologic mechanisms are vascular disease, membrane ruptures, infection, and autoimmunity. 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[3] reported vascular disorders as the underlying cause in the first large collection of 21 cases of SSNHL. In 1956, Hallberg[4] described the origin of SSNHL as a vascular accident in 50% of 178 patients.

Schuknecht et al[5] observed that alterations in the microcirculation of the cochlea may be a cause of SSNHL. In accordance with the theory of thromboembolism, abnormalities of rheological factors in the blood of patients with idiopathic SSNHL have been investigated, and reduced erythrocyte filterability,[6] high plasma viscosity, and high fibrinogen values have been reported to be associated with SSNHL.[7]

Histopathologic studies of human temporal bones have supported a vascular origin for SSNHL and sug-

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gested that the mechanisms for a vascular cause of SSNHL are hemorrhage, thrombosis, embolism, vasospasm, and hypercoagulability.[8-13]

On the other hand, the vascular theory of the pathogenesis of SSNHL is undermined by histopathologic findings in the temporal bones of patients with SSNHL, which show pathological alterations resembling viral labyrinthitis, and by the ineffectiveness of vasodilators, plasma expanders, rheoactive agents, and anticoagulants.[14-16] Various authors have refuted the hypothesis of hyperlipidemia as a pathogenic factor in SSNHL.[17,18]

Furthermore, in the literature there are only occasional reports of patients with SSNHL who have had high signal levels in the labyrinth on unenhanced magnetic resonance imaging, suggesting the possibility of a labyrinthine hemorrhage.[19,20]

Despite the controversies regarding a vascular cause of SSNHL, there are various studies concerning the role of vascular treatment based on the assumption that the clinical features of SSNHL are similar to those of other thromboembolic vascular diseases such as cerebral insult, myocardial infarction, or retinal ischemia. In particular, Suckfull et al[7] suggested that hyperfibrinogenemia and elevated erythrocyte aggregation may promote a prothrombotic or hypercoagulable state in patients with sudden hearing loss and may also be involved in the pathogenesis of SSNHL. But whether thromboembolic risk factors play a part in SSNHL is still unclear, and only a few studies on a small number of patients have been performed on SSNHL.

Thromboembolic risk factors can be grossly classified as congenital/inherited or acquired.[21] Acquired risk factors include age, male gender, malignancy, antiphospholipid antibodies, immobilization, paresis, venous catheters or a transvenous pacemaker, surgery, trauma, pregnancy and puerperium, and the use of oral contraceptives or hormone replacement therapy.[22,23] It is well recognized that myeloproliferative disorders such as essential thrombocythemia and polycythemia rubra vera may manifest themselves as venous thrombosis or ischemic stroke.[24]

Five or six well-defined inherited risk factors for venous thrombosis are known at present, but all together they can explain only part of the clustering of thrombotic events in families.[25] Antithrombin deficiency was discovered in the 1960s,[21] and protein C[26] and protein S[27] deficiencies were described in the 1980s. Resistance to activated protein C was described by Dahlbäck et al in 1993,[28] and the next year it was shown to be largely caused by a mutation in clotting factor V, termed factor V Leiden.[29] A mutation in the prothrombin gene found by Poort et al[30] in 1996 is associated with increased plasma concentrations of prothrombin and with an increased risk of thrombosis.

Mercier et al[31] and Patscheke et al[32] suggested the prothrombin G20210A mutation as a strong risk factor for SSNHL. Rudack et al[33] failed to find an association between these prothrombin and factor V mutations and reported platelet glycoprotein (GP)Ia (C807T) polymorphism associated with idiopathic SSNHL and a poor outcome, suggesting a pathophysiological model of platelet–vessel wall interactions in sudden hearing loss. These findings supported the role of thrombosis or microembolic events in the pathogenesis of SSNHL.

The aim of the present study was to evaluate the prevalence of thromboembolic acquired and congenital risk factors in a population of Italian patients with SSNHL.

MATERIALS AND METHODS

Patients. Forty-eight Italian patients affected by SSNHL were included in the study: 28 female (mean age, 50 years; range, 22 to 75 years) and 20 male (mean age, 46 years; range, 21 to 74 years). The exclusion criteria included a history of diabetes, stroke, cardiovascular disease, estrogen consumption, and vertigo. All patients had a history negative for familial deafness and metabolic diseases. All underwent a routine general physical examination. A total of 37 patients were nonsmokers, and 11 were regular smokers (more than 20 cigarettes per day). Only 2 of the patients were heavy drinkers (>1 L of wine per day); the remaining 46 patients consumed no more than 2 servings of wine per day.

We performed pure tone audiometry (frequencies 125, 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz; ISO standard), speech discrimination testing, impedance audiometry, auditory brain stem response testing, electronystagmography, computed dynamic posturography, and imaging (brain MRI, epi–aortic vessel ultrasound) in all patients. We used the following scale of hearing loss degree: mild, >20 to 40 dB hearing loss; moderate, >40 to 70 dB hearing loss; severe, >70 to 90 dB hearing loss; and profound, >90 dB hearing loss.

From the date of the hospitalization, all patients were treated with a combined regimen of steroids (1 mg/kg methylprednisolone daily) for 15 days, plasma expander (500 mL/d low–molecular weight dextran) for 5 days, and 100 mg/d acetylsalicylic acid for 15 days.

Hearing loss outcome was followed at least 6

months after onset of hearing loss. Hearing gains were used as parameters for hearing recovery. The hearing gain is an absolute value of hearing recovery representing the average change in hearing levels at the frequencies 250 to 4,000 Hz from before to after treatment. The Siegel classification was used to evaluate the outcome of patients in relation to the type and degree of hearing loss.[34] The Siegel classification is defined as follows: no improvement, less than 15 dB of gain; slight improvement, more than 15 dB of gain and a final hearing level poorer than 45 dB; moderate improvement, more than 15 dB of gain and a final hearing level between 25 and 45 dB; complete improvement, a hearing level better than 25 dB regardless of the amount of gain.

Controls. Forty-eight healthy Italian subjects without a history of hearing loss or autoimmune, metabolic, or circulatory diseases were included as matched controls; 20 were male (mean age, 41 years; range, 17 to 64 years) and 28 were female (mean age, 46 years; range, 23 to 67 years). Control subjects were recruited from clinic personnel and friends of patients. The patients and controls were unrelated. The presence of cardiovascular risk factors and other chronic diseases was assessed on the basis of the control subject's interview. Also, the controls had been examined specifically for cardiovascular risk factors and metabolic and autoimmune disorders at the time of recruitment. Chronic sensorineural hearing loss was excluded by pure tone audiometry after a routine otolaryngological examination. A total of 32 controls were nonsmokers, and 16 were regular smokers. All controls consumed no more than 2 servings 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: hemacytometric analysis including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, erythrocyte sedimentation rate, C-reactive protein, protein S, protein C, antithrombin III, and activated protein C resistance.

Laboratory tests (antiviral antibody titer) were also carried out to exclude viral infections such as cytomegalovirus, herpesvirus, Epstein-Barr virus, coxsackievirus, hepatitis B and C viruses, and venereal disease.

Genotypic Analyses. Informed consent was obtained from patients and controls. Venous blood was collected in tubes treated with ethylenediaminetetraacetic acid and centrifuged at room temperature for 15 minutes at 2,500*g*. The plasma supernatant was then removed and the pellet was stored at −70°C until DNA extraction was performed. Genomic DNA was isolated by using a DNA extraction kit (EXTRAcell, Amplimedical, Turin, Italy) according to the manufacturer's instructions.

The genetic polymorphisms factor V R506Q (G1691A), the prothrombin promoter G20210A, and the 5,10-methylenetetrahydrofolate reductase (MTHFR) A223V (C677T) were determined by using the Thrombophilia Panel Dot Blot Kit (Amplimedical), which is based on a multiple polymerase chain reaction analysis with allele-specific primers followed by hybridization with allele-specific oligonucleotides. Positive and negative controls, ie, samples from subjects with or without a known thrombophilic mutation, were always included.

Statistical Analyses. We used χ^2 (Yates correction) tests to compare the genotype distributions of inherited prothrombotic factors between patients and controls. Statistical significance was accepted with a p value of less than .05. Odds ratios and 95% confidence intervals were calculated for genotype frequencies of all prothrombotic variables. We also used χ^2 (Yates correction) analyses to compare allele frequencies of all factors between patients and controls. Statistical significance was accepted with a p value of less than .05. Odds ratios and 95% confidence intervals were calculated for allele frequencies of all prothrombotic variables. In order to evaluate the relationship between allele frequencies and hearing improvement, the patients with SSNHL were categorized into two outcome groups — a group with no or slight improvement and a group with complete or moderate improvement — in terms of hearing gain. Statistical analyses were performed with the software package EPI INFO version 3.3.2 (Centers for Disease Control and Prevention, Atlanta, Georgia).

RESULTS

The SSNHL was unilateral in 48 cases. Hearing loss was profound in 10 patients, severe in 19, moderate in 14, and mild in 5. No characteristic shape was detected: 30 patients had flat hearing loss, 12 had high-frequency hearing loss, 2 had U-shaped hearing loss, and 4 had low-frequency hearing loss. The presence of a retrocochlear lesion was excluded by means of auditory brain stem responses and magnetic resonance imaging in all patients. Normal vestibular reflectivity was present in all patients.

Results of virological and microbiological tests for herpesvirus, cytomegalovirus, influenza and parainfluenza, Epstein-Barr virus, coxsackievirus, hepatitis B and C viruses, and sexually transmitted diseases were negative in all patients. The results of the blood tests are given in Table 1.

No difference between patients and controls was

TABLE 1. BLOOD TEST RESULTS

Blood Test	*Patients With SSNHL*	*Healthy Control Subjects*
Fibrinogen (mg/dL)	260.4 ± 68.3	263.5 ± 69.0
Prothrombin time (International Normalized Ratio)	0.8 ± 0.2	0.9 ± 0.2
Activated partial thromboplastin time (s)	31.2 ± 7.8	30.7 ± 4.4
Platelet count ($\times 10^3/\mu L$)	231.3 ± 44.1	236.0 ± 40.8
D-dimer (ng/mL)	150.9 ± 76.6	142.8 ± 80.1
Antithrombin III (%)	103.5 ± 17.0	105.9 ± 14.8
Activated protein C resistance (s ratio)	1.0 ± 0.1	1.0 ± 0.1
Protein C (%)	118.7 ± 26.2	107.6 ± 16.3
Protein S (%)	83.5 ± 15.6	73.4 ± 9.0
Homocysteine (μmol/dL)	9.9 ± 6.2	8.3 ± 2.9

Data are mean ± SD.
SSNHL — sudden sensorineural hearing loss.

detected in hemacytometric analysis including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, erythrocyte sedimentation rate, C-reactive protein, protein S, protein C, antithrombin III, or activated protein C resistance.

The genotype distributions of factor V G1691A, prothrombin G20210A, and MTHFR C677T variants were not significantly different between patients and controls (Table 2). No significant differences in allele frequencies of factor V G1691A, factor II G20210A, and MTHFR C677T were detected between the group of patients with SSNHL and the healthy subjects (Table 2).

According to the Siegel classification, the hearing gain was slight in 2 patients with SSNHL, moderate in 3, and complete in 2; 41 cases had no improvement. No significant differences in allele frequencies of factor V G1691A, factor II G20210A, and MTHFR C677T were detected between either of the two hearing outcome groups of patients with SSNHL and the control subjects (see Materials and Methods).

DISCUSSION

One of the most accepted etiologic theories in SSNHL is the vascular one; nevertheless, the majority of cases are diagnosed on a basis of presumption. Our results show that SSNHL patients do not have major abnormalities in the most common thrombophilic factors. In our series, abnormal antithrombin III, protein C, protein S, D-dimer, and fibrinogen levels; activated protein C resistance; and factor V G1691A, factor II G20210A, and MTHFR C677T mutations were not associated with SSNHL.

At present, there are only 3 articles in the literature concerning genetic thrombophilic risk factors in patients with SSNHL.[31-33] Our data are not in accordance with the observations of Mercier et al[31] and Patscheke et al,[32] who suggested prothrombin G20210A mutation as a strong risk factor for SSNHL. In fact, we observed no significant difference in allele frequency between our patients and controls, in accord with Rudack et al.[33] It could be important to note that the relevance of the G20210A prothrombin allele as a risk factor for venous thromboembolism in the general population is still uncertain.[35]

Although it has been demonstrated that factor V (G1691A) represents a major intrinsic factor for cerebral sinus vein thrombosis,[36,37] we and Rudack et al[33] failed to demonstrate an association between the gene coding for factor V Leiden and SSNHL.

Hyperhomocysteinemia has also been identified as a risk factor for cerebrovascular, peripheral, and coronary vascular disease. Elevated levels of plasma homocysteine can result from genetic disturbances in the transsulfuration or remethylation pathways for homocysteine metabolism. In a previous study, we failed to demonstrate an association between hyperhomocysteinemia and SSNHL.[38] In the current study,

TABLE 2. ALLELE FREQUENCIES, GENOTYPE DISTRIBUTION, AND GENOTYPE FREQUENCIES FOR FACTOR V G1691A, PROTHROMBIN G20210A, AND MTHFR C677T IN SSNHL CASES AND CONTROLS

Gene	*Genotype*	*Patients*	*Controls*	*Allele Frequency in Patients*	*Allele Frequency in Controls*	*Comparison*	*Odds Ratio (95% CI)*	χ^2	*p*	*Comparison*	*Odds Ratio (95% CI)*	χ^2	*p*
Factor V G1691A	AA	0.0% (0)	0.0% (0)	1% (1)	2% (2)	A vs G				AA vs GA/GG			
	GA	2% (1)	4% (2)										
	GG	98% (47)	96% (46)	99% (95)	98% (94)								
Prothrombin G20210A	AA	0.0% (0)	0.0% (0)	2% (2)	1% (1)	A vs G				AA vs GA/GG	1	0.51	NS
	GA	4% (2)	2% (1)										
	GG	96% (46)	98% (47)	98% (98)	99% (95)								
MTHFR C677T	TT	14.5% (7)	14.5% (7)	50% (48)	51% (49)	T vs C	1 (0.57-1.76)	0.08	NS	TT vs CT/CC	1 (0.57-1.76)	0.08	NS
	CT	71% (34)	73% (35)										
	CC	14.5% (7)	12.5% (6)	50% (48)	49% (47)								

Odds ratios with 95% confidence intervals (CIs) and results (p values) of χ^2 analysis (Yates correction) were calculated for allele frequencies in patients compared with controls. Significance was accepted at $p < .05$.
MTHFR — 5,10-methylenetetrahydrofolate reductase; NS — not significant.

neither the MTHFR C677T polymorphisms nor the levels of serum homocysteine were elevated in patients with SSNHL compared with controls.

At present, studies regarding genetic polymorphisms of hemostatic factors in SSNHL are not conclusive. Epidemiological studies are needed to finally and significantly assess the role of hemostasis in this clinical setting.[39] Only international, multicenter, prospective, and well-designed studies will provide the currently lacking information and will gradually improve our knowledge in the field before the use of genetic polymorphism is implemented in the daily medical treatment of patients with SSNHL.

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