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ORIGINAL ARTICLE

Cardiovascular and thrombophilic risk factors for idiopathic sudden sensorineural hearing loss

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Summary. *Background:* In recent years there has been a significant increase in the diagnosis of sudden sensorineural hearing loss (SSHL) in western, countries with an incidence of 20 of 100 000 people affected every year. No clear causes for this disease have been found thus far, but cochlear ischemia has been hypothesized in patients in whom an infectious episode or acoustic neurinoma have been excluded. *Objectives:* The aim of this case–control study was to investigate a number of acquired and inherited thrombophilic risk factors [antithrombin, protein C and S; factor V (FV) Leiden, FII polymorphism; lupus anticoagulant (LA); anticardiolipin (aCL) antibodies; fasting homocysteine (Hcy); lipoprotein(a) (Lp(a)); plasminogen activator inhibitor-1 (PAI-1)] in addition to cardiovascular risk factors in patients with idiopathic SSHL (ISSHL). *Patients and methods:* We investigated 155 patients (67 male/88 female; age: 55 (range 19–79 years) with a diagnosis of ISSHL within 30 days from the onset of symptoms, and 155 controls (67 male/88 female; age 54 (range 19–78 years). Fasting Hcy levels were significantly higher in patients than in controls [11.6 (6.7–60) μmol/L vs. 8.7 (5.0–24) μmol/L] as well as PAI-1 levels [19 (2–95) mg/dL vs. 14.5 (4.0–87) mg/dL]. Lupus anticoagulant was present in 13 of 155 (8.4%) patients; 20 patients (12.9%) had positivity of aCL (four IgM and 16 IgG). In no patient was a deficiency of physiological clotting inhibitors antithrombin, protein C and protein S found. No significant differences between patients and controls were observed for Lp(a) plasma levels [111 (1–1146) mg/L vs. 103 (11–695) mg/L] and for the presence of FV Leiden (4.5% vs. 4.5%) and FII variant G20210A (3.8% vs. 3.2%). *Results and conclusions:* Independent risk factors for ISSHL at the multivariate analysis (adjusted for age, sex and the traditional cardiovascular risk factors) were the positivity of aCL: OR 5.6 (95% CI 2.0–15.3); cholesterol levels within the second and third tertiles (with respect to the first tertile): T2 = OR 4.8 (95% CI 1.9–12.6)/T3 = OR 19 (95% CI 7–50.1); PAI-1 and Hcy levels within the third tertile (with respect to the first tertile): OR 20 (95% CI 7.8–78) and OR 4.0 (95% CI 2.0–8.1), respectively. These preliminary data suggest that hypercholesterolemia, hyperhomocysteinemia, elevated PAI-1 levels and anticardiolipin antibodies are associated with ISSHL, so indirectly supporting the hypothesis of a vascular occlusion in the pathogenesis of the disease.

Keywords: hearing loss, homocysteine, risk factors, thrombophilia.

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) has an incidence of approximately 20/100 000 people per year, and young and otherwise healthy people are often affected.

The impairment site is usually localized in the cochlea, but some cases of retrocochlear lesions (e.g. cerebello pontine angle tumors, degenerative neural diseases, neuraxial ischemic lesions) can induce sensorineural deafness. The diagnosis of ISSHL [1,2] can be made definitively when no causes are found. Two main causes, viral and vascular, are considered in the origin of ISSHL [2]. The second, cochlear ischemia, has been related to alterations of cochlear microvessels [1,3,4]. This region is provided with a terminal capillary bed and is not able to form collateral vessels, which could restore blood flow in ischemic regions. Because cochlea has a high sensitivity to minimal blood flow reduction, occlusions at this level can lead to clinical manifestations [1]. Moreover, *in vivo* studies carried out in guinea pigs, in which impairment of cochlear blood flow was induced by ferromagnetic obstruction, showed that vascular obstruction in the inner ear resulted in a considerable reduction in intracochlear oxygenation, causing a significant loss in the auditory response [5]. Small infarctions of cochlear tissue associated with deafness have been observed in young subjects affected by multifocal microangiopathic encephalopathies [6]. Some studies have suggested that hemostatic and hemoreological alterations may be related to cochlear vascular occlusion [3,4,7–9]. More recently, an association between

hypoacusia and thrombophilic alterations has been also reported [3,10,11], but data on this issue are scarce, contrasting and often performed on a limited number of subjects.

The aim of this case–control study was to investigate the possible risk factors of ISSHL by evaluating a number of acquired and inherited thrombophilic risk factors in addition to the classical cardiovascular risk factors.

Materials and methods

Subjects investigated

One hundred and fifty-five (67 male/88 female; age: 54 (range 19–79 years) with a diagnosis of ISSHL referred to the Department of Audiology of Careggi University Hospital (Florence, Italy), were enrolled. All patients underwent complete audiological examination, complete history taking and general physical examination. The diagnosis of ISSHL was made by experienced audiologists by excluding other causes of sudden deafness such as viral, congenital, inflammatory, degenerative or traumatic.

The control population was of 155 sex- and age-matched subjects [67 male/88 female; age 54 (range 19–78 years)], friends or partners of patients, who volunteered to undergo laboratory investigations.

Exclusion criteria for patients and controls were any history of arterial or venous thrombotic disease or other chronic diseases. All subjects gave their informed consent for the experimental study, which was approved by the Institutional Review Board. The presence of traditional cardiovascular risk factors was assessed on the basis of patient's interview and hospital records.

Hypertension was defined as systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [12]; dyslipidemia was defined in the presence of total cholesterol levels $>$ 200 mg dL^{-1} and/or triglyceride levels $>$ 150 mg dL^{-1}, according to the Third Report of the National Cholesterol Education Program (NCEP) [13]; diabetes was defined in agreement with the American Diabetes Association [14].

Experimental procedure

Venous blood was collected within 30 days from the onset of symptoms, after an overnight fasting between 8 and 10 a.m. For determination of antithrombin (AT), protein C (PC), protein S (PS), plasminogen activator inhibitor-1 (PAI-1), lupus anticoagulant (LA) and lipoprotein (a) [Lp(a)], the first 2 mL of blood was discarded and blood samples were drawn in evacuated tubes (Vacutainer, Becton Dickinson, Meylan, France) containing a 0.129 mol L^{-1} concentration of sodium citrate (final ratio with blood 1 : 10). Blood samples were preserved and centrifuged at 4 °C (for PAI-1) or 18 °C (for AT, PC, PS, LA and Lp(a) measurement) (2000 ***g*** for 10 min) and frozen rapidly in liquid nitrogen and stored at −80 °C. Within 7 days, aliquots of plasma were thawed and used for determinations. AT and PC activities were evaluated by automated chromogenic methods (Dade, Behring, Marnurg, Germany). The levels of free PS (Asserachrom, Diagnostica Stago, Asnieres sur Seine, France), PAI-1 antigen (PAI-1 Asserachrom, Diagnostica Stago, Asnieres sur Seine, France) and Lp(a) [Apo(a) enzyme-linked immunosorbent assay (ELISA), Mercodia] were measured by ELISA. Platelet-poor plasma (PPP) for LA test was obtained by centrifuging blood samples twice at 1300 *g* for 10 min and was stored at −80 °C until used. The detection tests used for the presence of LA were: (1) diluted (1 : 50) aPTT (Pathromptin, Dade Behring); (2) kaolin clotting time (KCT, Diagnostica Stago); (3) tissue thromboplastin inhibition test (TITT, Dade Behring, using 1 : 1000 dilution); (4) dilute Russel's viper venom time [dRVVT; interleukin (IL) test LAC screening, Instrumentation Laboratory, Milan, Italy]. Mixing studies with normal plasma (pooled PPP from 20 normal subjects) were employed to exclude clotting factor deficiencies or the presence of antibodies against specific coagulation proteins. Specimens shown to be abnormal were also assayed according to the platelet neutralization procedure (PNP, Diagnostica Stago) as the confirmation test. We considered LA positive only those patients with tests confirmed by PNP. Sera for testing anticardiolipin antibodies (aCL) were obtained by centrifuging blood collected in evacuated tubes without anticoagulant at 1300 *g* for 10 min and stored at −20 °C. The aCL assay was performed by ELISA (first cardiolipin IgM and IgG, Eurospital, Trieste, Italy) and aCL levels were reported in anti IgG phospholipid (GPL) units (for IgG) and in anti IgM phospholipid (MPL) units (for IgM). On the basis of the analysis of several hundred normal serum specimens performed in our laboratory in the past, and according to the literature, values above 20 units for both IgG and IgM were considered abnormal. We considered antiphospholipid antibodies positive only in those patients with a test confirmed after at least 2 months. Hcy levels were measured by an immunoassay method (FPIA assay, IMx system, Abbott, IL, USA) on plasma samples obtained after centrifuging blood collected into tubes containing ethylenediamine tetra-acetic acid (EDTA_. For detection of factor V (FV) Leiden and G20210A polymorphism in the FII gene, genomic DNA was extracted from peripheral blood leukocytes using a MagNA Pure (Roche, Penzberg, Germany) and QUIAmp Blood Kit (Quiagen, Hilden, Germany), respectively. FV Leiden and G20210A polymorphism in the FII gene were identified by the light-cycler capillaries method (Roche).

Statistical analysis

Unless indicated otherwise, results are given as median (range). The non-parametric Mann–Whitney test for unpaired data was used for comparisons between single groups. Hypertension, smoking, aCL positivity (IgM $>$ 20 MPL and/or IgG $>$ 20 GPL), lupus anticoagulant, heterozygosity for FV Leiden and heterozygosity for FII polymorphism were used as dichotom-

ous variables. Cholesterol, triglycerides, Lp(a), Hcy and PAI-1 were divided in tertiles (based on the distribution in patients and controls). Univariate and multivariate analysis were used to describe the association between ISSHL and cholesterol, triglycerides, PAI-1, Lp(a), Hcy levels (second and third tertiles with respect to the first tertile), hypertension, smoking, aCL positivity, lupus anticoagulant, heterozygosity for FV Leiden and FII polymorphisms. Deficiencies of AT, PC and PS were not included in the logistic regression because no subject was found with these alterations. Diabetes was not included in the logistic regression as no control had diabetes. Lp(a) levels above 300 mg L^{-1}, a level associated with an increased risk of occlusive arterial disease, were considered over the normal range; high levels of Hcy and PAI-1 were diagnosed when plasma levels exceeded the 95th percentile of distribution of values obtained in controls (Hcy: 13 μmol/L in females and 19 μmol/L in males; PAI-1: 40 mg dL^{-1}).

All odds ratios (OR) are given with their 95% confidence interval. All probability values are two-tailed, with values of less than 0.05 considered statistically significant.

Results

Clinical characteristics of subjects investigated are shown in Table 1. Among the classical risk factors for vascular disease, the incidence of hypercholesterolemia and hypertriglyceridemia was higher among patients with respect to controls (Table 1). Thrombophilic risk factors investigated in ISSHL patients and control subjects are shown in Table 2.

AT, PC and PS levels were similar in patients and controls (Table 2) and in no patient was a deficiency of physiological clotting inhibitors antithrombin, PC and PS found. In patients fasting Hcy levels were higher than in controls [11.6 (6.7–60) μmol/L vs. 8.7 (5.0–24) micromol/L], as well as PAI-1 levels [19 (2–95) mg/dL vs. 14.5 (4–87) mg/dL] (Table 2). The incidence of hyperhomocysteinemia was 29/155 (18.7%) among patients (15 of 882 females and 14 of 67 males) and eight of 155 (5.1%) among controls (four of 88 females and four of 67 males). PAI-1 levels above the 95th percentile of controls were documented in 31 of 155 (20%) patients and in eight of 155 (5.1%) controls. Lupus anticoagulant was present in 13 of 155 (8.4%) patients; 20 patients (12.9%) had a positivity of aCL (four IgM and 16 IgG). No differences between patients and controls were observed for Lp(a) plasma levels [111 (1–1146) mg/L vs. 103 (11–695) mg/L] (Table 2); 36 patients (23.2%) and 22 controls (14.2%) had Lp(a) levels above 300 mg L^{-1}. The presence of FV Leiden and FII variant 20210GA was not more prevalent in patients with respect to controls (4.5% vs. 4.5% and 3.8% vs. 3.2%, respectively) (Table 2). Both FV Leiden and FII polymorphism genotype distribution in controls were compatible with the Hardy–Weinberg equilibrium. Thrombophilic risk factors investigated were not significantly different in the subgroup of patients < 45 years (Table 2).

Independent risk factors for ISSHL at the multivariate analysis (adjusted for age, sex, hypertension, smoking, cholesterol and triglyceride levels) were the positivity of aCL: OR 5.6 (95% CI 2.0–15.3); cholesterol levels within the second and third tertiles (with respect to the first tertile): T2 = OR 4.8 (95% CI 1.9–12.6)/T3 = OR 19 (95% CI 7–50.1); PAI-1 and Hcy levels within the third tertile (with respect to the first tertile): OR 20 (95% CI 7.8–78) and OR 4.0 (95% CI 2.0–8.1), respectively (Table 3).

Table 1 Clinical and laboratory characteristics of subjects investigated

	ISSHL $n = 155$	Controls $n = 155$
Hypertension	25 (16.1)	18 (11.6)
Smoking	21 (13.5)	23 (14.8)
Diabetes mellitus	3 (1.9)	–
Hypercholesterolemia	52 (33.5)	11 (7.0)
Hypertriglyceridemia	31 (20)	8 (5.1)
Oral contraceptives*	4 (4.5)	2 (2.2)
Hormone replacement therapy*	5 (5.6)	8 (9.0)
Menopause*	45 (51.1)	39 (44.3)

Data are expressed as *n* (%).
*The percentage was calculated on the subgroup of females ($n = 88$).

Table 2 Thrombophilic risk factors in patients and controls

	Patients ($n = 155$)	Patients < 45 years ($n = 58$)	Controls ($n = 155$)
Heterozygosity for FV Leiden (n,%)	7 (4.5)	2 (3.4)	7 (4.5)
Heterozygosity for FII polymorphism (n,%)	6 (3.8)	2 (3.4)	5 (3.2)
Antithrombin (%)	108 (77–140)	101 (80–135)	107 (74–140)
Free protein S (%)	97 (70–153)	95 (70–140)	97.5 (69–153)
Protein C (%)	138 (81–217)	130 (85–200)	138 (81–2167)
Lupus anticoagulant (n,%)	13 (8.4)	5 (8.6)	1 (0.6)
ACL IgM (UMPL)	2.8 (0.5–33.4)	3.0 (1–32)	3.0 (1.1–6.1)
ACL IgG (UGPL)	6.6 (1.3–56.1)	6.1 (1.5–46)	4.8 (2.6–36.1)
Hcy (μmol/L)	11.6 (6.7–60)	11 (5–51)	8.7 (5.0–24)
Lp(a) (mg/L)	111 (1–1146)	120 (30–48)	103 (11–695)
PAI-1 (mg/dL)	19 (2–95)	18 (10–81)	14.5 (4–87)

Data are expressed as median (range).

Discussion

The pathogenesis of ISSHL is unknown, even if viral infections and vascular occlusions are the most frequent mechanisms hypothesized to explain its occurrence. To support vascular occlusion, an impaired cochlear perfusion is a widely accepted hypothesis, although the location of cochlea in the temporal bone makes the identification of a thrombotic occlusion difficult [1,2]. In order to identify possible risk factors which are commonly linked to an impaired vascular perfusion in regions different from the cochlear region, during recent years a limited number of studies has evaluated the possible role of different cardiovascular and thrombophilic factors in the pathogenesis of ISSHL. However, all the available studies have assessed one or only a few factors, often in a limited number of patients [3,4,7–11,15–17]. This is the first study

Table 3 Univariate and multivariate analysis

	Univariate analysis (OR 95% CI)	Multivariate analysis‡ (OR 95% CI)
Hypertension	0.7 (0.4–1.3)	0.4 (0.1–0.9)
Smoking	0.9 (0.5–1.7)	1.3 (0.5–3.4)
Cholesterol (mg/dL)¶		
T1 (< 147)	1	1
T2 (148–190)	7.0 (3.4–14.0)*	4.8 (1.9–12.6)*
T3 (> 190)	19 (10–38.6)*	19 (7–50.1)*
Triglycerides (mg/dL)¶		
T1 (< 82)	1	1
T2 (82–98)	0.9 (0.5–1.5)	0.6 (0.4–1.3)
T3 (> 98)	12.8 (6.4–27)*	3.0 (0.3–42)
PAI-1 (mg/dL)¶		
T1 (< 11.7)	1	1
T2 (11.7–25)	0.5 (0.2–1.3)	1.2 (0.4–3.0)
T3 (> 25)	6.4 (2.3–18)*	20 (7.8–78)*
Homocysteine (μmol/L)¶		
T1 (< 8.9)	1	1
T2 (8.9–11)	1.2 (0.7–2.0)	0.8 (0.4–1.5)
T3 (> 11)	3.9 (2.8–6.8)*	4.0 (2.0–8.1)*
Lp(a) (mg/L)¶		
T1 (< 67)	1	1
T2 (68–163)	1.4 (0.8–3.0)	1.2 (0.5–2.53)
T3 (> 163)	1.8 (1.1–3.0)*	1.8 (0.5–4.1)
Lupus anticoagulant	15.9 (2.0–123)†	3.6 (0.3–43.3)
aCL positivity§	6.0 (2.0–18.2)*	5.6 (2.0–15.3)†
Heterozygosity for FV Leiden	1.0 (0.3–2.9)	0.6 (0.2–3.5)
Heterozygosity for FII polymorphism	1.3 (0.3–5.0)	0.7 (0.05–6.0)

‡Adjusted for age, sex, hypertension, smoking, cholesterol and triglycerides levels.
†$P < 0.005$; *$P < 0.0001$.
§aCL IgM > 20 MPL and/or aCL IgG > 20 GPL.
¶First tertile (T1) as the reference group.

which has thoroughly evaluated the most important cardiovascular and thrombophilic risk factors in a large number of patients with ISSHL. The results obtained in our study have identified a number of risk factors significantly associated with ISSHL.

Among the cardiovascular risk factors, a relevant role has been documented for dyslipidemia. High levels of both total cholesterol and triglycerides are more prevalent in ISSHL patients with respect to controls, but at multivariate analysis only hypercholesterolemia remained an independent risk factor for ISSHL. Hypercholesterolemia is a well-established risk factor for atherosclerosis and is associated with vascular occlusion of large arteries in the coronary, cerebral and peripheral regions [18–20]. It is conceivable a similar role in the impairment of cochlear perfusion, which is a vascular region provided with a terminal capillary bed. Furthermore, in animal models affected by hypercholesterolemia, the presence of alterations was demonstrated in cochlear ultrastructures consisting of profound edema in the strial marginal layer and slight edema in the outer hair cells [21,22].

Among other parameters investigated, we found an independent association between ISSHL and hyperhomocysteinemia, elevated PAI-1 levels and anticardiolipin antibodies which are not clear, or sole, prothrombotic abnormalities.

No data are available in the literature on Hcy levels in patients with ISSHL. Hcy is an amino acid whose role as risk factor for coronary, cerebrovascular and peripheral artery disease has been well documented [23–25], even if contrasting results are available on the clinical effect of its pharmacological correction [26–28]. Genetic and environmental factors are responsible for high Hcy levels: in particular, a number of polymorphisms in genes coding for enzymes involved in Hcy metabolism has been found to be associated with high Hcy levels, the first C677T polymorphism in the gene coding for methylenetetrahydrofolate reductase (MTHFR) [29]. On the other hand, low levels of the vitamins which act as cofactors of the enzymes involved—folic acid, vitamin B_6 and vitamin B_{12}—are the other main cause of hyperhomocysteinemia [30]. Interestingly, recent studies have documented a role of folic acid deficiency as a cardiovascular risk factor independently of Hcy levels [31]. Only a single study performed on 43 ISSHL patients [15] is available in the literature in which lower folate levels were observed in patients with respect to controls. Our results revealed a possible therapeutic target, as high levels of Hcy may be lowered easily by a vitamin supplementation based on folic acid, vitamin B_6 and B_{12}.

Our results on PAI-1 levels underline the possible role of fibrinolysis in ISSHL. Only one previous report on 25 patients with ISSHL [17] has investigated fibrinolysis and has reported high PAI-1 levels in seven patients. Elevated PAI-1 levels, resulting in impaired fibrinolysis, are an unclear and controversial risk factor for venous thrombosis, whereas they may be predictive of the future development of atherothrombosis [32,33]. Furthermore, elevated PAI-1 levels are related to the presence of dyslipidemia (both hypercholesterolemia and hypertriglyceridemia), low physical activity and high body mass index [34]. Accordingly, in our study the incidence of elevated PAI-1 and dyslipidemia are increased significantly in ISSHL patients, but remained risk factors at the multivariate analysis independently from one other.

Our findings on the high incidence of lupus anticoagulant and anticardiolipin antibodies confirm data from studies performed on a lower number of patients [35–37]. However, until now no study had evaluated lupus anticoagulant and aCL antibodies in the same patients. In the most recent and large available study, performed on 51 patients with ISSHL, the authors [36] found an incidence of 31% for aCL antibody positivity in the acute phase, whereas the lack of aCL antibody persistence after 3 months in as many as half the patients suggested strongly that transient phenomena (e.g. viral infection) may trigger aCL antibody activity. On the other hand, ISSHL is a rarely reported manifestation of systemic lupus erythematosus [38,39]. This condition has been seen most frequently in individuals with concomitant antiphospholipid syndrome, although a direct causal relationship remains unconfirmed. ISSHL may be caused by autoimmune disorders localized in the inner ear or secondary to systemic immune diseases. Our data suggest that aCL are an independent risk

factor for ISSHL and therefore may play an important role in the pathogenesis of this disability. The incidence of antiphospholipid antibodies found in our patients is probably overestimated, as it is based on a single aCL and LA determination which could have been influenced by a transient inflammatory state. On the other hand, the concomitant corticosteroids administered to the majority of our patients could have decreased the titre of autoantibodies investigated. aCL, PAI-1 and Lp(a) levels also act as acute phase proteins. Even if we studied our patients within 30 days from the onset of symptoms, further studies will be needed to confirm our results at a longer interval from the acute event.

Finally, no role has been documented for anticoagulant deficiencies and thrombophilic polymorphisms, FV Leiden and prothrombin G20210A in the pathogenesis of ISSHL. A previous report [9] on 118 German patients has documented a significantly higher incidence of prothrombin G20210A in ISSHL with respect to controls, whereas FV Leiden was not associated with the disease. Furthermore, the incidence of prothrombin G20210A was even higher in the subgroup of young patients (< 40 years of age). Our study, performed in Italian patients, could not confirm those results. We repeated our analysis on the incidence of all cardiovascular and thrombophilic risk factors in the subgroup of young patients (58 of 155 with ISSHL < 45 years of age), but we did not document any significant difference with respect to the whole group.

In summary, our ISSHL patients had no increased incidence of 'true' prothrombotic abnormalities, whereas they were more often hypercholesterolemic, therefore suggesting the possible role of a pro-atherogenic alteration in ISSHL. On the other hand, there are some inconsistencies in our findings because other cardiovascular risk factors (such as smoking and hypertension) had a similar incidence in patients and controls. Moreover, the role of the positive findings—hyperhomocysteinemia, elevated PAI-1 levels and anticardiolipin antibodies—in ISSHL also need to be clarified by further studies.

Contribution of authors

Study design: D.P., R.M.; clinical evaluation of patients: P.B., E.L., P.P.; laboratory investigations: A.A.L., A.P.C., A.R.; statistical analysis: R.M.; writing up: R.M., R.A., D.P.

References

1 Mom T, Avan P, Gilian L. Les surdités brusques idiopathiques. *Rev Méd Interne* 2002; **23**: 292–307.
2 Mattox DE, Lyles CA. Idiopathic sudden sensorineural hearing loss. *Am J Otol* 1989; **10**: 242–7.
3 Lalanne MC, Doutremepuich C, Boj F, Traissac L, Quichaud F. Some hemostatic and hemorheological disorders in auditory and vestibular impairments. *Thromb Res* 1992; **66**: 787–91.
4 Einer H, Tengborn L, Axelsson A, Edstrom S. Sudden sensorineural hearing loss and hemostatic mechanisms. *Arch Otolaryngol Head Neck Surg* 1994; **120**: 536–40.
5 Scheibe F, Haupt H, Baumgartl H. Effects of experimental cochlear thrombosis on oxygenation and auditory function of the inner ear. *Eur Arch Otorhinolaryngol* 1997; **254**: 91–4.
6 Schwitter J, Agosti R, Ott P, Kalman A, Waespe W. Small infarctions of cochlear, retinal, and encephalic tissue in young women. *Stroke* 1992; **23**: 903–7.
7 Browning GG, Gatehouse S, Lowe GDO. Blood viscosity as a factor in sensorineural hearing impairment. *Lancet* 1986; **1**: 121–3.
8 Ohinata Y, Makimoto K, Kawakami M, Haginomori S, Araki M, Takahashi H. Blood viscosity and plasma viscosity in patients with sudden deafness. *Acta Otolaryngol* 1994; **114**: 601–7.
9 Patscheke JH, Arndt J, Dietz K, Zenner HP, Reuner KH. The prothrombin G20210A mutation is a risk factor for sudden hearing loss in young patients. *Thromb Haemost* 2001; **86**: 1118–9.
10 Gold S, Kamerer DB, Hirsch BE, Cass SP. Hypercoagulability in otologic patients. *Am J Otolaryngol* 1993; **14**: 327–31.
11 Mercier E, Quere I, Chabert R, Lallemant JG, Daures JP, Berlan J, Gris JP. The 20210A allele of the prothrombin gene is an independent risk factor for perception deafness in patients with venous thromboembolic antecedents. *Blood* 1999; **93**: 3150–2.
12 Chobainian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JRJL, Jones DW, Materson BJ, Oparil S, Wright JJT, Roccella JT. The seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–71.
13 Anonymous. Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adult (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143–421.
14 Anonymous. Reports of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; **26**: S5–20.
15 Cadoni G, Agostino S, Scipione S, Galli J. Low serum folate levels: a risk factor for sudden sensorineural hearing loss? *Acta Otolaryngol* 2004; **124**: 608–11.
16 Toubi E, Ben-David J, Kessel A, Podoshin L, Golan TD. Autoimmune aberration in sudden sensorineural hearing loss: association with anti-cardiolipin antibodies. *Lupus* 1997; **6**: 540–2.
17 Wang MS, Wang XX, Chen XD, Chen JF. Study on the coagulation state of sudden deafness. *Lin Chuang Er Bi Yan Hou Ke Za Zhi* 2000; **14**: 305–7.
18 Gensini GF, Comeglio M, Colella A. Classical risk factors and emerging elements in the risk profile for coronary artery disease. *Eur Heart J* 1998; **19** (Suppl. A): A53–61.
19 Leys D, Deplanque D, Mounier-Vehier C, Mackowiak-Cordoliani MA, Lucas C, Bordet R. Stroke prevention: management of modifiable vascular risk factors. *J Neurol* 2002; **249**: 507–17.
20 Kim CK, Schmalfuss CM, Schofield RS, Sheps DS. Pharmacological treatment of patients with peripheral arterial disease. *Drugs* 2003; **63**: 637–47.
21 Satar B, Ozkaptan Y, Surucu HS, Ozturk H. Ultrastructural effects of hypercholesterolemia on the cochlea. *Otol Neurotol* 2001; **22**: 786–9.
22 Suzuki K, Kaneko M, Murai K. Influence of serum lipids on auditory function. *Laryngoscope* 2000; **110**: 1736–8.
23 Cattaneo M. Hyperhomocysteinemia and atherothrombosis. *Ann Med* 2000; **32**: 46–52.
24 Schwammenthal Y, Tanne D. Homocysteine, B-vitamin supplementation, and stroke prevention: from observational to interventional trials. *Lancet Neurol* 2004; **3**: 493–5.
25 Darius H, Pittrow D, Habert R, Trampisch HJ, Schuster A, Lange S, Tepohl HG, Allenberg JL, Diehm C. Are elevated homocysteine plasma levels related to peripheral arterial disease? Results from a cross-sectional study of 6880 primary care patients. *Eur J Clin Invest* 2003; **33**: 751–7.
26 Schnyder G, Roffi M, Flammer Y, Lange H, Eberli FR, Meier B, Turi ZG, Hess OM. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med* 2001; **345**: 1593–600.

27 Lange H, Suryapranata H, De Luca G, Borner C, Dille J, Kallmayer K, Pasalary MN, Scherer E, Dambrink JH. Folate therapy and in-stent restenosis after coronary stenting. *N Engl J Med* 2004; **350**: 2673–81.
28 Marcucci R, Zanazi M, Bertoni E, Rosati A, Fedi S, Lenti M, Prisco D, Castellani S, Abbate R, Salvadori M. Vitamin supplementation reduces the progression of atherosclerosis in hyperhomocysteinemic renal-transplant recipients. *Transplantation* 2003; **75**: 1551–5.
29 Abbate R, Sardi I, Pepe G, Marcucci R, Brunelli T, Prisco D, Fatini C, Capanni M, Simonetti I, Gensini GF. The high prevalence of thermolabile 5–10 methylenetetrahydrofolate reductasa (MTHFR) in Italians is not associated to an increased risk for coronary artery disease (CAD). *Thromb Haemost* 1998; **79**: 727–30.
30 Selhub J. Homocysteine metabolism. *Annu Rev Nutr* 1999; **19**: 217–46.
31 Selhub J. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. *J Nutr Health Aging* 2002; **6**: 39–42.
32 Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. *N Engl J Med* 2000; **342**: 1792–801.
33 Lijnen HR. Pleiotropic functions of plasminogen activator inhibitor-1. *J Thromb Haemost* 2005; **3**: 35–45.
34 Kaba NK, Francis CW, Moss AJ, Zareba W, Oakes D, Knox KL, Fernandez ID, Rainwater DL, THROMBO Investigators. Effects of lipids and lipid-lowering therapy on hemostatic factors in patients with myocardial infarction. *J Thromb Haemost* 2004; **2**: 718–25.
35 Krysiak R, Okopien B, Herman Z. Effects of HMG-CoA reductase inhibitors on coagulation and fibrinolysis processes. *Drugs* 2003; **63**: 1821–54.
36 Green L, Miller EB. Sudden sensorineural hearing loss as a first manifestation of systemic lupus erythematosus: association with anticardiolipin antibodies. *Clin Rheumatol* 2001; **20**: 220–2.
37 Toubi E, Ben-David J, Kessel A, Halas K, Sabo E, Luntz M. Immune-mediated disorders associated with idiopathic sudden sensorineural hearing loss. *Ann Otol Rhimol Laryngol* 2004; **113**: 45–49.
38 Chapman J, Rand JH, Brey RL, Levine SR, Blatt I, Khamashta MA, Shoenfeld Y. Non-stroke neurological syndromes associated with antiphospholipid antibodies: evaluation of clinical and experimental studies. *Lupus* 2003; **12**: 514–7.
39 Naarendorp M, Spiera H. Sudden sensorineural hearing loss in patients with systemic lupus erythematosus or lupus-like syndromes and antiphospholipid antibodies. *J Rheumatol* 1998; **25**: 589–92.