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Risk factors for idiopathic sudden sensorineural hearing loss and their association with clinical outcome

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ABSTRACT

Background: Sudden sensorineural hearing loss (ISSHL) is idiopathic in 85% of cases and cochlear microthrombosis has been hypothesized as pathogenic mechanism. The role of thrombophilia and cardiovascular risk factors in ISSHL is controversial and whether these risk factors influence the clinical outcome of ISSHL is unknown.

Methods: and patients To investigate the role of thrombophilia and cardiovascular risk factors in ISSHL and to evaluate their influence on clinical outcome of the disease, 118 patients with a first episode of ISSHL and 415 healthy controls were investigated. Thrombophilia screening included measurements of antithrombin, protein C, protein S, factor V Leiden, prothrombin G20210A, antiphospholipid antibodies, fibrinogen, factor VIII and homocysteine.

Results: Deficiencies of antithrombin, protein C or S taken together, high factor VIII and hyperhomocysteinemia were significantly associated with ISSHL (OR [95%CI]: 7.55 [1.05-54.47], 2.91 [1.31-6.44] and 2.69 [1.09-6.62], respectively), whereas no association was found with the remaining thrombophilia markers. A 2-fold increased risk of poor clinical outcome was observed for every 5 μmol/L increase of fasting homocysteine levels (adjusted OR [95%CI]) 2.13 [1.02-4.44]) until levels of approximately 15 μmol/L, then the risk increased slowly. Cardiovascular risk factors (arterial hypertension, hyperlipidemia, diabetes and smoking) were associated with an increased risk of ISSHL (OR [95%CI] 1.88 [1.17-3.03]) and with a poor clinical outcome (OR [95%CI] 2.22 [0.93-5.26]).

Conclusions: Hyperhomocysteinemia, high factor VIII and, with more uncertainty, deficiencies of antithrombin, protein C or S and cardiovascular risk factors increase the risk of ISSHL. Hyperhomocysteinemia and cardiovascular risk factors are associated with a poor clinical outcome of ISSHL.

Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined as a sudden hearing impairment of more than 30 dB HL across three contiguous frequencies within a period of 72 hours. It occurs preferentially in the fourth decade of life, with equal sex distribution and an annual incidence that varies between 5 and 20 cases in 100.000 individuals [1]. Approximately 1% of cases of ISSHL are due to retrococlear diseases that may be related to vestibular schwannoma, demyelinating diseases or stroke [1]. Another 10-15% of cases are due to other causes, such as Ménière syndrome, autoimmune or infectious diseases (e.g., syphilis or Lyme disease), and traumas. In the remaining 85% of cases ISSHL is considered idiopathic and cochlear vascular micro-thrombosis has been hypothesized as pathogenic mechanism despite no objective test can detect the occlusion of such a microcirculation [2]. The diagnosis of ISSHL requires a complete audiogram, including threshold measurement of bone and air conducted pure tones and speech audiometry and MRI of the temporal bone and brain to rule out a retrococlear abnormality. Because in most cases the aetiology of ISSHL remains unknown, various therapeutic approaches have been considered, such as hyperbaric oxygen therapy, oral corticosteroids, aspirin, low molecular weight heparin, citicoline and pentoxyphilline, with overall poor efficacy [1,3]. The likelihood of recovery varies according to the severity of hearing loss at presentation, having patients with mild hearing losses a better prognosis than those with severe-to-profound losses [4,5].

Because of the micro-vascular occlusive hypothesis, hypercoagulability, due to thrombophilia abnormalities or common venous (oral contraceptive use, pregnancy/puerperium) or cardiovascular (arterial hypertension, hyperlipidemia, diabetes and cigarette smoking) risk factors, can be investigated in patients with ISSHL. Thrombophilia abnormalities are either inherited, i.e., deficiencies of the natural anticoagulant proteins antithrombin, protein C and protein S and the gain-of-function mutations in the factor V (factor V Leiden) and prothrombin genes, or

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acquired, i.e., the presence of antiphospholipid antibodies [6,7]. Two other thrombophilia abnormalities whose inheritance is not clearly demonstrated are high plasma levels of factor VIII and mild-to-moderate hyperhomocysteinemia (HHcy), a metabolic disorder due to an impairment of conversion of the aminoacid methionine into cysteine [6]. Finally, circulating microparticles, submicroscopic phospholipid-rich particles released from platelets, endothelial cells, leucocytes and erythrocytes can also be considered as potential risk factors for ISSHL, as they are associated with an increased risk of thrombosis [8,9].

So far, few studies investigated the role of thrombophilia and other risk factors for thrombosis in patients with ISSHL, showing conflicting results [10–18]. Only one study addressed the impact of thrombophilia and cardiovascular risk factors on the clinical outcome of ISSHL [15]. This case–control study was aimed to investigate the role of thrombophilia, microparticles and other risk factors for thrombosis in patients with idiopathic ISSHL. In addition, we evaluated whether the presence of risk factors for ISSHL could be predictive of the clinical outcome of the disease.

Material and Methods

Study Population

One-hundred and twenty-four patients consecutively referred to our Thrombosis Center between August 2004 and June 2013 for a thrombophilia screening after a first episode of ISSHL were investigated at least three months after ISSHL to avoid the possible interference of the acute phase on some coagulation blood tests. Six patients were excluded because the diagnostic work-up revealed the presence of cerebral ischemic lesions in four, autoimmune diseases in one and a recent head trauma in another one. Hence, the final study population included 118 patients with idiopathic ISSHL. Diagnosis of ISSHL was made by an audiologist with otomicroscopy, vestibular evaluation, complete audiological examination by pure-tone audiometry with measurement of air conduction at all octave frequencies between 125 and 8000 Hz and of bone conduction thresholds at 250 to 4000 Hz, immittance audiometry and speech audiometry, MRI of the temporal bone and brain. Inflammatory, viral and autoimmune diseases were investigated. Type and duration of therapies and timing of audiologic control visits were decided by the audiologist who made the diagnosis of ISSHL. Severity of ISSHL was defined as mild, moderate, severe and profound as previously described [4,5] and recovery after four weeks was defined complete (within 10 dB HL of contralateral ear hearing pure tones), partial (50% or more) or absent (less than 50%), according to published criteria [19,20].

Four-hundred and fifteen healthy individuals who were partners or friends of the whole population of patients referred to our Thrombosis Center formed the control group. They were recruited during the same period of patients and had never had ISSHL or thrombosis [21].

Demographic data, medical history, use of oral contraceptives, pregnancy/puerperium, arterial hypertension (systolic pressure >140 mmHg; diastolic pressure >90 mmHg) [22], hyperlipidemia (total cholesterol levels >200 mg/dL and/or triglyceride levels >150 mg/dL) [23], diabetes (fasting plasma glucose levels >126 mg/dL) [24], cigarette smoking (current versus non current smoking), ISSHL therapies and clinical outcome of ISSHL were recorded. No patient or control was on anticoagulant therapy at the time of blood sampling. The study was approved by the Hospital Institutional Review Board, and all patients and controls gave a written informed consent to participate to the study. Results are reported in accordance with the STROBE guidelines [25].

Laboratory Tests

Patients and controls were tested for thrombophilia screening that included measurements of antithrombin, protein C, protein S, factor V Leiden, prothrombin G20210A, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein 1 IgG and IgM antibodies), fibrinogen, factor VIII and homocysteine. Tests were performed on citrated plasma, serum or DNA, as appropriate and previously described in details [26]. Plasma homocysteine was measured both at fasting and after a methionine load of 3.8 g per square-meter of body surface area, and HHcy was defined when levels exceeded the 95th percentile of the homocysteine distribution among controls (17 and 22 μmol/L fasting and 28 and 29 μmol/L the difference between post-methionine load and fasting, for females and males, respectively). High factor VIII plasma levels were defined when exceeding the 95th percentile of the distribution among controls (166 IU/dL). Microparticles were measured in plasma as previously described [27]. Blood count, cholesterol (total and high density lipoprotein), triglycerides, glucose, serum cyanocobalamin and folic acid were also measured.

Statistical Analysis

Assuming a 5% prevalence of HHcy, factor V Leiden or prothrombin G20210A (the most common thrombophilic abnormalities) among controls, with a case:control ratio of 1:4, a two-tailed α error of 0.05 and a 80% of power, we calculated a minimal statistically significant relative risk of 3.15 with a sample size of 100 ISSHL patients and 400 controls. Continuous variables were expressed as median with interquartile range (IQR), and categorical variables as count and percentage. Comparison between groups was made by Mann–Whitney U test for continuous variables, and by Chi square test for categorical variables. To assess which predictor was associated with the risk of ISSHL, a multivariable logistic regression model containing thrombophilia abnormalities (antithrombin, protein C or protein S deficiency, factor V Leiden, prothrombin G20210A, factor VIII, HHcy), cardiovascular risk factors (defined as the presence of at least one of the following: arterial hypertension, hyperlipidemia, diabetes or cigarette smoking), sex and age was fitted. Odds ratios (OR) and 95% confidence intervals (CI) were calculated as an estimate of the risk of ISSHL in carriers relative to non-carriers of the risk factor adjusting for the confounding effect of the other covariates. Homocysteine and factor VIII were tested both as categorical (according to the definition of HHcy and high factor VIII given above) and as continuous variables (for homocysteine both fasting and the difference between post-methionine load and fasting plasma levels), using a restricted cubic spline function (with three knots) to assess possible deviations from linearity in the logit. Those variables associated with ISSHL were studied in another multivariable logistic model to assess their association with ISSHL recovery (complete or partial versus absent) after therapies. $P \leq 0.05$ was chosen as cut-off for statistical significance. All statistical analyses were performed with the statistical softwares SPSS (release 20.0; SPSS, Chicago, IL, USA) and R (release 3.0.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

The main characteristics of the study population are shown in Table 1. Patients were slightly older than controls and presented tinnitus as first symptom in three quarters of cases, either in left or in right ear. Twenty patients (17%) had severe-profound hearing loss or deafness at the onset of ISSHL. No patient had a positive personal history or arterial or venous thrombosis and 6% of patients had at least one first-or second-degree family member with arterial or venous thrombosis at an age <45 years. Almost half of the patients had no venous or cardiovascular risk factors at the time of ISSHL. Overall, thrombophilia abnormalities were found in 31% of patients and 16% of controls, with HHcy as the most prevalent one. HHcy was diagnosed for high fasting plasma levels in 9 patients and 13 controls and for high post-methionine load levels in 10 patients and 12 controls. HHcy was determined, at least in part, by low levels of cyanocobalamin or folic acid in 5 patients and no controls. Fibrinogen levels were similar in patients and controls (median levels [IQR]: 299 [267–339] mg/dL and 295 [257–339] mg/dL, respectively; $p = 0.721$). Among other risk factors for thrombosis, arterial hypertension, hyperlipidemia and smoking were