Idiopathic Sudden Sensorineural Hearing Loss: Classic Cardiovascular and New Genetic Risk Factors

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Abstract

\textbf{Background:} The main causative process in idiopathic sudden sensorineural hearing loss (iSSNHL) has yet to be explained or demonstrated. The clinical picture supports vascular involvement, but obvious limitations of inner ear study make this difficult to corroborate. \textbf{Objectives:} To determine the role of thrombophilic genetic variants that may affect platelet function and to assess the cardiovascular risk profile in a cohort of patients with iSSNHL. \textbf{Patients and Methods:} 118 Caucasian patients with iSSNHL were recruited from the same geographical area and enrolled prospectively in this study. Clinical data were obtained for each patient. Polymorphisms of the platelet glycoprotein subunit IIa gene, ITGB3 (PLA1/A2, rs5918), and of the platelet glycoprotein subunit la gene, ITGA2 (C807T, rs1126643) were analyzed. A control group of 161 age- and gender-matched healthy individuals from the same geographical area was recruited for genetic comparisons. In order to determine the cardiovascular risk profile of each patient and of our cohort, a cross-sectional assessment was performed by means of a calibrated Framingham coronary heart disease risk scale. Risk factor proportions were compared to those recommended in European guidelines for coronary prevention, which are also based on the Framingham function. \textbf{Results:} A significantly high prevalence of the 807T allele of platelet glycoprotein subunit la was found in patients compared to controls. There was a significant correlation between the 807TT homozygous genotype and a low probability of recovery. The PLA1/A2 polymorphism of platelet glycoprotein subunit IIa was not associated with recovery, with a similar genotype prevalence being found in patients and controls. In terms of cardiovascular risk profile, patients did not present an excess of baseline coronary risk factors compared to the general population in the same geographical area. \textbf{Conclusions:} Patients with iSSNHL had a higher prevalence of the 807T thrombophilic polymorphism of platelet glycoprotein IIa/IIa. Patients homozygous for this polymorphism are less likely to recover from iSSNHL. Classical cardiovascular risk factors were not related to iSSNHL.

Key Words
Cardiovascular risk factors · Thrombophilia · DNA polymorphisms · Framingham study · Acquired risk factors · Platelet polymorphism · Platelet glycoproteins · Idiopathic sudden sensorineural hearing loss · Sudden deafness

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Introduction

Idiopathic sudden sensorineural hearing loss (iSSNHL) is a common medical emergency defined as a sensorineural hearing loss of ≥30 dB in at least three sequential frequencies in the standard pure-tone audiogram occurring within ≤3 days [Byl, 1984]. The incidence of iSSNHL in developed countries is estimated to be 5–20 cases per 100,000 inhabitants per year [Byl, 1984], although a more recent study put the figure at 150 cases per 100,000 per year [Suckfüll, 2007]. A wide age range and no gender preference are the main demographic features. There is a peak incidence between 50 and 60 years of age, although the problem may present in healthy young adults in whom no recognized risk factors of iSSNHL are present. Vascular occlusion, viral or autoimmune disorders, ruptured inner ear membrane, and fat metabolic disorders have been proposed as global causes of iSSNHL. Approximately 1% of cases are due to retrocochlear disorders that may be related to acoustic neuroma, demyelinic diseases or stroke. In another 10–15%, iSSNHL appears as part of the symptoms presenting with Ménière’s disease, trauma, autoimmune disease, syphilis, Lyme disease or perilymphatic fistula. The remaining cases are idiopathic [Gussen, 1976; Jaffe, 1978; Goodhill, 1980; Rauch, 2008; Wieling et al., 2009]. Although iSSNHL is currently assumed to be multicausal, recent studies have proposed vascular occlusion as the main causative process in the inner ear in cases of iSSNHL and early hearing loss [Suckfüll, 2002; Grgic et al., 2005; Rudack et al., 2006; Rauch, 2008; Zhuo et al., 2008; Wieling et al., 2009; Shargorodsky et al., 2010]. Blood circulation in the inner ear is an end-functional system. Anatomical features explain the extreme sensitivity of the cochlea to vascular perfusion and the variability of the clinical picture seen in some patients (presence of vertigo, tinnitus or both, different audiogram shape drop, etc.). The first branch of the internal auditory artery is the anterior vestibular artery, which supplies the posterior and lateral semi-circular canals, the utricle and the posterior part of the saccule. The cochlea is supplied by the spiral modiolar artery and the vestibulocochlear artery, which supplies the apex, second turn and part of the basal turn of the cochlea. The vestibulocochlear artery gives off a vestibular branch and a cochlear branch (which feeds the proximal part of the base of cochlea). As the arteries travel they decrease in size and lose their muscular layer, increasing their susceptibility to abnormalities in peripheral vasomotor regulation [Schuknecht, 1974; Mom et al., 2005].

The factors contributing to the variable vascular involvement in iSSNHL are not fully understood, although genetic factors affecting platelet receptors may play a role. Genetic polymorphisms that affect the platelet receptors involved in adhesion processes have been related to an increased risk of arterial thrombosis. Platelet glycoprotein (GP) Ia/Ila is the major platelet collagen receptor and is responsible for platelet adhesion to the exposed vessel wall. The C807T polymorphism of the Ia subunit (ITGA2 gene, rs1266463) has been related to GP Ia/Ila receptor expression [Kunicki et al., 1997; Moshfegh et al., 1999], with T allele carriers having increased receptor density and thrombotic risk [Pellitero et al., 2010; Guella et al., 2011; Yonal et al., 2012]. GP IIb/IIIa is the main platelet surface receptor for fibrinogen. The PLA1/2 polymorphism in the IIIa subunit (ITGB3 gene, rs5918) has been related to thrombotic risk, while the prothrombotic allele PLA2 has been associated with atherothrombotic risk [Bentley et al., 2010; Pellitero et al., 2010; Kucharska-Newton et al., 2011]. However, two large meta-analyses on the role of the PLA1/2 polymorphism in coronary disease have reached opposing conclusions [Zhu et al., 2000; Di Castelnuovo et al., 2001].

Although a relationship between a polymorphism of this platelet GP and iSSNHL has been suggested, its role is not fully elucidated [Rudack et al., 2004].

The aim of the present study was to analyze the classical cardiovascular risk profile in a cohort of patients with iSSNHL using the Framingham REGICOR risk score, and to determine whether there was an association between platelet receptor polymorphisms and iSSNHL occurrence and outcome.

Materials and Methods

From a total of 167 patients, 118 patients with iSSNHL were included in this prospective study from 1994 to 2008. In all cases, iSSNHL was diagnosed by clinical history, otomicroscopy, tympanometry, and standard pure-tone audiometry. Data on clinical and demographic characteristics, lifestyle variables, medication, family history, vascular risk factors, and past medical history were obtained by means of a standard questionnaire. All subjects included in the study were from the same geographical area (Barcelona, Spain) and had a normal coagulation screening (prothrombin time, thrombin time and activated partial thromboplastin time, fibrinogen level, and platelet count), which was performed by standard methods.

In all patients, gadolinium-enhanced magnetic resonance imaging (MRI) was performed to rule out retrocochlear diseases. Additional screening tests (blood analyses including hemogram, antiphospholipid antibodies, Lyme disease, syphilis, and lipid profile) were included to rule out well-known causes of iSSNHL.
Patients with a diagnosis of iSSNHL secondary to primary or secondary antiphospholipid syndrome, multiple sclerosis, systemic lupus erythematosus (SLE), acoustic neuroma, syphilis or Lyme disease were excluded.

For the purposes of this study, the severity of hearing loss was categorized as mild (21–40 dB), moderate (41–70 dB), severe (71–90 dB) or profound (>90 dB). Recovery was defined as a restoration of hearing (similar hearing thresholds compared with the contralateral ear). Partial recovery was defined as an improvement in the audiogram shape over 20 dB but without complete restoration of hearing thresholds.

The selected control group (n = 161) had similar demographic features (median age and gender ratio) and was selected from the same geographical area so as to avoid differences in ethnic composition compared to patients with iSSNHL. All patients gave their informed consent to participate in the study.

All patients with iSSNHL received an early intravenous treatment with corticosteroids (methylprednisolone 2 mg/kg/12 h/5 days). In the majority of patients, a systemic vasodilator (butlomedil hydrochloride 50 mg/8 h/5 days) was added to the treatment, which was withheld in those cases presenting persistent arterial hypotension since the onset of iSSNHL. Patients seen within 1 week of SSNHL onset received 5 days of endovenous treatment. After the first week, patients received oral corticosteroids (1 mg/kg/day). Treatment effectiveness was monitored by serial pure-tone audiograms for at least 6 months after onset of iSSNHL.

Cardiovascular Risk Assessment

The risk of cardiovascular disease was assessed in 96 patients by means of the Framingham REGICOR risk score (calibrated Framingham function for the Spanish population) [Marrugat et al., 2003a]. For study purposes, our cohort of affected patients was subdivided into four main groups according to age and age-related risk of cardiovascular events in our area (group 1: 35–44 years; group 2: 45–54 years; group 3: 55–64 years, and group 4: 65–74 years). Patients <35 or >74 years of age (n = 22) were excluded from this analysis.

Genetic Analyses

During hospitalization, venous blood samples were obtained from a clean antecubital venipuncture without vein occlusion and collected into tubes containing 3.8% trisodium citrate (Becton, Dickinson and Company, Rutherford, N.J., USA). Genomic DNA was extracted from 100 ml of whole blood by a silica gel column method (QIAamp DNA blood mini kit; Qiagen GmbH, Hilden, Germany).

Analysis of the 807 C/T polymorphism of GP Ia/IIa was performed by PCR-restriction fragment length polymorphism, as previously reported [Jiménez et al., 2008]. The following primers were used: 5'-TTC TGA TTG CTG GAC TTC TCT T-3' (sense) and 5'-TCT CTC CCC ATG GCA AAG AGT-3' (antisense). PCR was carried out on 50-milliliter volume samples, with 40 cycles at 95°C for 120 s, at 58°C for 60 s, and at 72°C for 120 s. PCR products were digested with 20 U of MspI (Roche Diagnostics) for 16 h at 65°C. Detection was by means of 2% agarose gel electrophoresis. The expected sizes of the products were 221 and 45 bp for the PLA1 allele and 177, 50, and 45 bp for the PLA2 allele [Jin et al., 1993].

Results

Of the 167 potential participants, 118 patients were enrolled in the study, all of whom met the accepted criteria for iSSNHL. Sixty-three patients were males (53.4%) and 55 were females (46.6%); gender ratio was 1.1 to 1. Median age was 52 ± 14 years, with a range between 15 and 88 years. The control group (n = 161) had a median age of 53.4 ± 28 years and a gender ratio of 1 to 1.

At onset, 6% of patients had mild levels of hearing loss, 41% moderate, 39% severe, and 14% profound. No side predominance was noted (46.8% in the right ear and 53.2% in the left). Two patients (2%) had bilateral iSSNHL with normal screening studies. Forty-nine patients did not meet the inclusion criteria as their SSNHL was secondary to another condition: in the majority of these cases, SSNHL was detected within the context of Ramsay-Hunt syndrome, ponto-cerebellar angle tumors, multiple sclerosis or SLE. All these cases showed a normal coagulation screening.

At onset, 33.1% of patients presented vertigo (defined as a sensation of rotation or movement of oneself or one’s surroundings in any plane). Dizziness (defined as a painless head discomfort related to balance) was found in 11%, while 69.5% had tinnitus and 30% ear fullness. Tinnitus and vertigo together were found in 28% of cases. The average time elapsed between onset and treatment in the whole series was 7.4 ± 7.2 days. Eight patients (6.8%) con-
Table 1. Baseline characteristics of patients compared with other published series

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</thead>
<tbody>
<tr>
<td>Median age ± SD, years</td>
<td>52 ± 14</td>
<td>50 ± 30</td>
<td>51 ± 17</td>
<td>61.6 ± 2</td>
<td>n.r.</td>
<td>48.1 ± 14</td>
<td>54 ± 25</td>
<td>50 ± 14</td>
</tr>
<tr>
<td>Gender ratio, M/F</td>
<td>1/1.1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>n.r.</td>
<td>1/1</td>
<td>1/1.2</td>
<td>1/1.1</td>
</tr>
<tr>
<td>Tinnitus, %</td>
<td>65.5</td>
<td>57</td>
<td>74.6</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Vestibular disturbances, %</td>
<td>44.1</td>
<td>39</td>
<td>31.7</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Pathological MRI, %</td>
<td>2</td>
<td>n.r.</td>
<td>5.6</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
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<tr>
<td>Total cholesterol, mg/dl</td>
<td>217 ± 44</td>
<td>14.5₁</td>
<td>215 ± 32</td>
<td>n.r.</td>
<td>0.8₁</td>
<td>224 ± 38</td>
<td>33.5₈</td>
<td>213 ± 44</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>58 ± 19</td>
<td>n.r.</td>
<td>61 ± 2</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>132 ± 11</td>
<td>n.r.</td>
<td>114 ± 29</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Lp(a), mg/dl</td>
<td>37 ± 41</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>111 n.r.</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>30.5</td>
<td>25</td>
<td>56.3</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>13.5 n.r.</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>21.1</td>
<td>19.7</td>
<td>14.1</td>
<td>n.r.</td>
<td>8.4</td>
<td>n.r.</td>
<td>16.1 n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Hypotension, %</td>
<td>8.8</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>7</td>
<td>4</td>
<td>5.6</td>
<td>n.r.</td>
<td>10.1</td>
<td>n.r.</td>
<td>1.9</td>
<td>n.r.</td>
</tr>
<tr>
<td>BMI</td>
<td>26.2 ± 4</td>
<td>25 ± 1.2</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
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<tr>
<td>LAC, %</td>
<td>4.2</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>8.4</td>
<td>n.r.</td>
</tr>
<tr>
<td>Control group, n</td>
<td>160</td>
<td>179</td>
<td>84</td>
<td>2141</td>
<td>5692</td>
<td>200</td>
<td>155</td>
<td>43</td>
</tr>
</tbody>
</table>

All means are shown with SD. Lp(a) = Lipoprotein(a); BMI = body mass index; LAC = lupus anticoagulant; n.r. = not reported.

₁ Proportion of high cholesterol patients expressed as a percentage.

Table 2. Descriptive variables according to Framingham cardiovascular risk scales [Marrugat et al., 2003a]

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>35–44 years</th>
<th>45–54 years</th>
<th>55–64 years</th>
<th>65–74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases per group</td>
<td></td>
<td>20</td>
<td>43</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>6 (30%)</td>
<td>21 (49%)</td>
<td>10 (62%)</td>
<td>11 (77%)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>14 (70%)</td>
<td>22 (51%)</td>
<td>6 (38%)</td>
<td>4 (23%)</td>
</tr>
<tr>
<td>Ratio M/F</td>
<td></td>
<td>1/2</td>
<td>1/1</td>
<td>1.5/1</td>
<td>3/1</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td>8 (40%)</td>
<td>9 (20.9%)</td>
<td>9 (56.2%)</td>
<td>3 (18.1%)</td>
</tr>
<tr>
<td>High blood pressure (&gt;120–129/80–84 mm Hg)</td>
<td></td>
<td>3 (15%)</td>
<td>9 (20.9%)</td>
<td>6 (37.5%)</td>
<td>10 (68.1%)</td>
</tr>
<tr>
<td>Total cholesterol (&gt;220 mg/dl)</td>
<td></td>
<td>6 (30%)</td>
<td>8 (18.6%)</td>
<td>7 (43.7%)</td>
<td>7 (45.4%)</td>
</tr>
<tr>
<td>HDL cholesterol₇ (&lt;35 mg/dl)</td>
<td></td>
<td>0 (0%)</td>
<td>1 (2.3%)</td>
<td>1 (6.2%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Diabetesb</td>
<td></td>
<td>1 (5%)</td>
<td>5 (11.6%)</td>
<td>2 (12.5%)</td>
<td>4 (22.7%)</td>
</tr>
<tr>
<td>Framingham risk scorec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>20 (23%)</td>
<td>34 (35%)</td>
<td>8 (8%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Slight</td>
<td></td>
<td>1 (1%)</td>
<td>7 (7.6%)</td>
<td>6 (6%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>0</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Very high</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

₇ If HDL cholesterol <35 mg/dl, real risk ×1.5; if HDL cholesterol >60 mg/dl, real risk ×0.5. b Includes diabetes mellitus I and II and altered glycemia levels, after fasting plasma glucose test, in mg/dl (over 126 and 100–126, respectively). c Risk factors evaluated (HDL cholesterol, mg/dl; systolic blood pressure, mm Hg; diabetes mellitus I and II and altered glycemia levels, mg/dl; age, years; smoker; gender) and individual risk at 10 years by means of calibrated Framingham score sheets. Risk categories for major coronary heart disease (myocardial infarction or coronary death) at 10 years of follow-up are defined as low (<5%), slight (5–9%), moderate (10–19%), high (20–39%), and very high (>39%).
resulted >2 weeks after the onset of iSSNHL. When excluding these patients, the time elapsed between onset and treatment was 2.5 ± 2.8 days.

Hearing was recovered by 16.1% of patients, while partial hearing recovery was observed in 24.6%, and 59.3% showed no improvement. After the onset of iSSNHL, chronic tinnitus (defined as tinnitus for >6 months) and vertigo were observed in 11%. The mean time from diagnosis to restoration of pure-tone thresholds was 13 weeks.

Table 1 shows otological findings and baseline clinical features of our patients. Cardiovascular risk scores (calibrated Framingham score adapted to the Spanish population) and proportions of each classical risk factor are shown in table 2. It can be seen that the patients' cardiovascular risk ranged from low to moderate, with no patients in the high or very high cardiovascular risk groups.

**Platelet Polymorphisms**

The prevalence of genotypes and allele frequencies in patients and controls are shown in table 3. Patients had a higher T allele frequency than controls (p = 0.005). The presence of one or two T alleles (807TT + 807CT vs. 807CC) was associated with iSSNHL (p = 0.004; OR 1.97; 95% CI 1.12–3.21). The relationship between platelet polymorphisms and iSSNHL recovery is shown in table 4.

Homzygous 807TT carriers (807TT vs. 807CT + 807CC) had a higher probability of no recovery (p = 0.03; OR 4.67; 95% CI 1.01–22.33). There was no positive association between recovery and the prevalence of the thrombophilic allele (PLA2 polymorphism).

**Discussion**

The results of this study reveal a relationship between the platelet glycoprotein Ia/IIa C807T polymorphism and iSSNHL onset and outcome.

After a vascular injury, platelet surface glycoprotein receptors are known to bind rapidly to exposed subendothelial extracellular matrix proteins. The adhesion of platelets to the vascular wall is mediated by platelet GP Ia-IIa. In fact, this receptor is mostly linked to subendothelial collagen. A dimorphism at position 807 (C807T) in the gene for subunit Ia ITGA2 leads to an increased receptor density on the platelet surface [Kunicki, 1998], and the 807 allele has been associated with acute myocardial infarction and/or stroke in younger individuals [Zozt et al., 1998; Croft et al., 1999; Santos et al., 1999].

Here, we found a statistically significant difference in 807T allele frequency between patients and controls. Moreover, the presence of the T allele was correlated with a lower probability of recovery, especially in homozygous carriers.

Our results are consistent with those reported by Rudack et al. [2004], who analyzed eight different polymor-
phisms in 85 patients with sudden hearing loss and found a relationship between the 807T allele and recovery of hearing level after treatment. As in our series, no differences were found with respect to the PLA polymorphism.

The platelet receptor GP IIb-IIIa is involved in platelet-platelet aggregation by binding fibrinogen between adjacent platelets. A polymorphism of the IIa subunit (PL A1/A2) is found in approximately 15% of the white population [Croft et al., 1999; Santosolo et al., 1999; Rudack et al., 2004]. An increased risk of acute coronary thrombosis has been associated with the PLA2 allele in some studies [Santosolo et al., 1999; Rudack et al., 2004], although its role in arterial thrombosis remains controversial [Weiss et al., 1996; Croft et al., 1999]. Our homozygous carriers of PLA2 tended to have poorer recovery rates after treatment, but this was not significant, a finding that fails to replicate the significant difference observed in this regard by Rudack et al. [2004]. However, our results are consistent with those of Capaccio et al. [2005], who did not find a higher prevalence of the A2 allele in the case group compared to controls.

In two previous papers by our group, we demonstrated the synergy between the two thrombophilic alleles of C807T and PLA1/A2 as assessed in patients with diabetes and in those with antiphospholipid syndrome or SLE [Jiménez et al., 2008; Pellitero et al., 2010]. Here, patients with antiphospholipid syndrome who carried both polymorphisms had a greater risk for arterial thrombosis, while patients with SLE who carried both polymorphisms were more at risk of arteriosclerosis [Jiménez et al., 2008]. Similarly, patients with type 2 diabetes who carried both polymorphisms had an increased risk for both clinical and subclinical cardiovascular disease [Pellitero et al., 2010]. In the present study, 19 patients were double heterozygous for both polymorphisms, and none of them showed hearing recovery.

We have previously reported on a series of 99 patients presenting the single nucleotide polymorphism Factor V Leiden (R506Q) and the prothrombin polymorphism (PT G20210A), and found no significant relationship to iSSNHL [Ballesteros et al., 2009], a finding that confirms the results of Mosnier et al. [2011] and Marcucci et al. [2005]. However, it should be noted that the selection criteria and screening of non-idiopathic causes of iSSNHL in the paper by Marcucci et al. [2005] are unclear. In terms of the specific literature on these two coagulation polymorphisms, Mercier et al. [1999] and Patscheke et al. [2001] have demonstrated their deleterious role in patients with iSSNHL.

In our setting, Spain, patients with iSSNHL often delay seeking specialized medical attention, with the majority of cases being seen in primary care and non-specialist departments. Generally, patients are not seen by an ear, nose and throat (ENT) specialist until several days after the onset of symptoms, and routine tympanometry and audiometry tests are not performed then. Some authors report a correlation between delayed treatment of iSSNHL and poor prognosis [Byl, 1984; Rauch et al., 2008], although others have demonstrated that a treatment delay does not necessarily influence the final degree of hearing loss as long as treatment is started within 24 h to 1 week of onset [Huy and Sauvaget, 2005]. As all our patients eventually received treatment, we cannot infer how many of them would have improved spontaneously without any therapeutic intervention.

With minor differences, our main epidemiological and outcome results are consistent with previous reports, particularly as regards gender, age heterogeneity, the affected side, audiogram patterns, presence of dizziness/vertigo/tinnitus, and time elapsed to ENT specialist consultation [Mattox and Simmons, 1977; Huy and Sauvaget, 2005; Sakata and Kato, 2006; Nosrati-Zarenoe et al., 2007; Moon et al., 2009].

As regards vascular features, our data are broadly in line with previously published epidemiological results. Unfortunately, the lack of certain specific data does not enable full comparisons between these series [Capaccio et al., 2005; Marcucci et al., 2005; Rudack et al., 2006; Lin et al., 2008; Cadoni et al., 2010; Uchida et al., 2010; Mosnier et al., 2011]. Analogous data were observed in other studies for the cardiovascular and neurovascular risk profiles [Capaccio et al., 2005; Marcucci et al., 2005; Rudack et al., 2006; Lin et al., 2008; Cadoni et al., 2010; Uchida et al., 2010; Mosnier et al., 2011]. Lin et al. [2008] compared the presence of stroke in cohorts of appendectomy and iSSNHL patients. However, the age range of patients makes it difficult to determine the mean and the real range of distribution. Additionally, this study does not distinguish between patients with SSNHL and iSSNHL. Furthermore, only 0.8% of the cohort described by Lin et al. [2008] had hyperlipidemia, whereas in European studies, cholesterol levels are higher than in their control groups [Capaccio et al., 2005; Marcucci et al., 2005; Rudack et al., 2006; Cadoni et al., 2010; Mosnier et al., 2011]. In our sample, 28% of patients had total cholesterol levels >220 mg/dl. In our view, these differences can be explained by environmental influences linked to classical cardiovascular risk factors. For example, the mean age of patients in the study by Uchida et al. [2010] was about 10
years higher than in studies conducted in Europe [Capacci et al., 2005; Marcucci et al., 2005; Rudack et al., 2006; Cadoni et al., 2010; Mosnier et al., 2011]. Despite these differences, however, our case group did not show an excess of cardiovascular risk factors.

A surprising finding in the present study was that during the follow-up period, 6 patients (3.6%) with a median age of 71 years (range 62–81) were diagnosed with atrial fibrillation (AF). AF causes approximately 25% of strokes in the elderly population. Given that cardioembolic stroke has been proposed as a risk factor in some cases of SSHL [Hyung et al., 2002; Gerace et al., 2008], we might also consider iSSNHL to be a minor symptom of stroke in some cases among older people. However, the presence of acute AF onset in iSSNHL was not the object of assessment in the present study.

Risk of Coronary Heart Disease and iSSNHL

To date, no studies have clinically evaluated cardiovascular and neurovascular risk factors. The risk of developing coronary heart disease depends on several factors, some associated with lifestyle and operating from early childhood onward. Many of these determinants interact in a nonlinear fashion, making individual assessment complicated, especially in younger people. In our study, a cross-sectional assessment was performed in patients between 35 and 74 years of age. As we have shown, the cohort of patients with iSSNHL does not appear to accumulate excessively high risk scores, this being true even for our elderly patients. Despite the limited number of patients (n = 96), we nonetheless made a comparison with recommended proportions of combined risk factors in European guidelines for coronary prevention. This analysis revealed no significant differences between our case group and the general population [Marrugat et al., 2003b].

The poorer risk scores observed may be explained by considering iSSNHL as an epiphenomenon or a minor symptom of a vascular occlusive disease, rather than as a potential cardiovascular risk factor in itself. In our view, patients with higher scores (high and very high risk of coronary heart disease) are probably more likely to suffer a serious cardiovascular event than an iSSNHL. In addition, the gender ratio of iSSNHL among elderly patients is 3:1 in favor of men, whereas the incidence of cardiovascular disease tends to be the same in men and women of advanced age [Marrugat et al., 2003b]. These findings do not support our hypothesis that iSSNHL might be considered a prodromal symptom of vascular occlusive disease.

Finally, another interesting finding of our study was the association between iSSNHL and arterial hypotension in younger adults. Eleven patients (9.3%), all except one aged < 52 years of age, showed persistent lower blood pressure levels. They had no history of hypertension drug intake. There was also one 62-year-old patient who presented a bradycardia syndrome. These results are consistent with those of a previous small case-control study [Pirodda et al., 2001]. In our opinion, severe arterial hypotension or, hemodynamically, a poorly tolerated arterial hypotension may, especially in the case of older adults, be considered a risk factor for iSSNHL. Identification of these cases at onset could be important because many treatment protocols for iSSNHL include vasodilators [Labus et al., 2010; Agarwal and Pothier, 2009].

Conclusions

The C807T thrombophilic polymorphism of platelet glycoprotein Ia/IIa is more prevalent in patients with iSSNHL. Homozygosis for this polymorphism is related to a lower probability of recovering previous hearing thresholds. In terms of the cardiovascular risk profile, patients with iSSNHL do not accumulate an excess of baseline coronary risk factors compared to the general population from the same geographical area.

Disclosure Statement

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