Endothelial dysfunction in idiopathic sudden sensorineural hearing loss: a review

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Abstract

An endothelial dysfunction has been described in idiopathic sudden sensorineural hearing loss (ISSHL) patients. The purpose of our review was to: i) identify, evaluate and review recent research about cardiovascular risk factors involvement and signs of endothelial dysfunction in ISSHL; ii) implication of these discovering in clinical practice and future research. A Medline literature search was conducted to identify any study on the involvement of endothelial dysfunction in ISSHL, published in the English language in the last decade. The following MEDLINE search terms were used: *sudden sensorineural hearing loss* (SSHL) and *endothelial dysfunction* (text words). Additional studies were identified by hand searching the references of original articles and review articles. Studies were not excluded on the basis of the qualitative or quantitative definitions of SSHL, treatment regimens, or outcome measures. Data were extracted from included papers by a reviewer. Information on the patients, investigations, methods, interventions, and outcomes were systematically analyzed. Characteristics and results of all included studies were reviewed systematically. High levels of adhesion molecules, hyperhomocysteinemia and lower folate levels, unbalanced oxidative status, a lower value of flow-mediated dilatation of brachial artery and a reduced percentage of circulating endothelial progenitor cells in patients affected by ISSHL support the hypothesis that this syndrome should be considered as a microcirculation disorder based on endothelial dysfunction and drive clinicians to implement all the traditional strategies used for preventing cardiovascular events, to also reduce the likelihood of ISSHL occurrence.

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is defined according to American Academy of Otolaryngology as a hearing loss of at least 30 dB over 3 contiguous test frequencies occurring within a 72-h period.[1] It affects 5 to 20 people per 100,000 annually and is characterized by sudden-onset, generally unilateral, sensorineural hearing loss.[2] Its cause is idiopathic in most of the patients; however, vascular disorders have been proposed as the final common pathway.[3]

To date, little is known about the pathogenesis of ISSHL, but there is a general consensus that it is a syndrome rather than a disease, ascribable to a range of different causes.[4] Among these are numbered viral diseases, immune mediated processes and vascular injury.[5] The hypothesis that a disturbance of the cochlear microcirculation could be at the basis of the different triggering conditions stems from the observation that sudden hearing loss has an acute onset, is generally unilateral and can resolve within a few hours or days.[6] The sudden onset of the hearing loss, usually unilateral, and the possible spontaneous recovery suggest a vascular involvement.[7] Experimental evidence has also shown that the cochlear microcirculation is highly sensitive to variations in blood flow and even mild hypoperfusion can lead to immediate loss of function of the organ of Corti.[6] In addition findings of abnormal red cell filterability,[8] and increased plasma and whole blood viscosity[9] in ISSHL patients have been described more than 20 years suggesting a vascular involvement. It is known that endothelial dysfunction has a prime role in regulating vascular tone by modifying lipoproteins, thrombogenesis and transformation of circulating monocytes into foam cells[10] and that endothelial dysfunction precedes the onset of atherosclerosis.

The purpose of this review was to: i) identify, evaluate and review recent research about cardiovascular risk factors involvement and signs of endothelial dysfunction in ISSHL; ii) implication of these discovering in clinical practice and future research.

Materials and Methods

A MEDLINE literature search was conducted to identify any study on the involvement of endothelial dysfunction in ISSHL, published in the English language in the last decade. The following MEDLINE

search terms were used: *sudden sensorineural hearing loss* (SSHL) and *endothelial dysfunction* (text words). Additional studies were identified by hand searching the references of original articles and review articles.

Studies were not excluded on the basis of the qualitative or quantitative definitions of SSHL, treatment regimens, or outcome measures. Data were extracted from included papers by a reviewer. Information on the patients, investigations, methods, interventions, and outcomes were recorded on a standardized data collection form.

Characteristics and results of all included studies were reviewed systematically.

Results

Role of oxidative stress

Recent studies have reported that the impaired microvascular perfusion occurring during an ischemic event may be related not only to traditional vascular risk factors such as hypercholesterolemia, hyperfibrinogenemia, hyperhomocysteinemia and micro embolisms,[11,12] but also to oxidative stress which may be synergistically responsible for endothelial damage, especially in terminal microvascular systems.[11,13] In order to evaluate a subject's oxidative stress condition, characterized by excessive production of oxidants and/or depletion of physiological antioxidant defense systems, Oxy-I, a new diagnostic tool reflecting an overall pro-oxidant/anti-oxidant exposure balance, appeared to be more appropriate and useful than a single parameter.[11,14] In fact, Capaccio and colleagues,[11] in their observational study, evaluated the role of oxidative stress in ISSHL. In thirty-nine ISSHL patients and seventy healthy subjects serum reactive oxygen species concentrations (ROS) and total antioxidant capacity were measured by spectro-photometric methods on F.R.E.E. analyzer (Diacron International, Grosseto, Italy). Moreover, a global oxidative stress index (Oxidative-INDEX), reflecting both oxidative and antioxidant counterparts, was also calculated. 25/39 patients showed oxidative stress due to ROS levels significantly higher than controls (348.2±84.8 *vs* 306.75±46.7 UCarr; P=0.001). The Oxidative-INDEX was significantly higher in patients than in controls (0.75±2.4 *vs* –0.0007±1.28 AU, P=0.03). As oxidative stress is a key determinant in endothelial dysfunction, their findings could suggest vascular impairment involvement in ISSHL.

In a successive pioneering study, Cadoni and colleagues have described also an association of ISSHL and low serum levels of the antioxidant of Co-enzyme Q (CoQ),[15] but, as in the opinion of authors, further studies needed to investigate the role of antioxidants, including CoQ, in ISSHL.

The role of soluble adhesion molecules and cytokines

One of the first signs of an endothelial dysfunction is increased expression of the molecules mediating adhesion of the leukocytes to the endothelial cells and triggering the atherogenic process.[16] In particular, E-selectin together with P-selectin favor delayed leukocyte circulation and rolling on the endothelial surface. As activated endothelial cells increase the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), the monocytes remain strongly adherent to the activated cells, inducing an altered hemorheologic status.[16,17]

Two prospective studies investigated the role of soluble adhesion molecules in pathogenesis of ISSHL. Basing on a case report of a patient affected by ISSHL with high levels of circulating adhesion molecules,[18] Quaranta and colleagues evaluated the concentration of soluble ICAM-1 (sICAM-1) and soluble VCAM-1 (sVCAM-1) in 37 patients affected by ISSHL.[17]

Inclusion criteria for the study were hearing loss of more than 30 dB hearing level affecting at least 3 contiguous frequencies, normal hearing on the contralateral ear, negative history of hearing loss or ear surgery in the affected ear, and magnetic resonance with gadolinium negative for VIII cranial nerve pathologic findings. Circulating levels of sICAM-1 and sVCAM-1 were evaluated by means of enzyme-linked immunosorbent assay. The levels of adhesion molecules in SSHL patients were compared with those of a control group.

sICAM-1 and sVCAM-1 levels in serum of patients with ISSHL were significantly higher than those of the matched control subjects (P<0.001). Statistical analysis did not show significant differences between the 2 groups in terms of the known vascular risk factors such as total and fractionated cholesterol, triglycerides, fibrinogen, erythrocyte sedimentation rate (ESR), smoking and diabetes. The results of the study showed that in ISSHL patients, there is an increased expression of circulating adhesion molecules confirming the existence of an endothelial dysfunction and supporting the vascular involvement in the pathogenesis of the disease.

The factors responsible for the endothelium activation in ISSHL patients are, however, still unknown; in fact, other known vascular risk factors that may increase adhesion molecule expression (diabetes, hypertension, smoking, obesity) were equally represented in ISSHL patients and controls. The fact that elevated adhesion molecules in ISSHL patients did not correlate with the hearing status in the affected and non-affected ears confirmed that further studies were needed in order to define the trigger factors responsible for the clinical presentation.

On the contrary, Haubner and colleagues,[19] in their case-control study with planned data collection, analyzed blood samples of 35 patients presenting with ISSHL and compared ISSHL group to a gender- and age-matched control group of normal-hearing subjects. Levels of the sICAM-1, sVCAM-1, endothelial selectin (E-selectin), and concentration of interleukin 6 (IL-6), interleukin 8 (IL-8) and monocyte chemoattractant protein 1 (MCP-1) were measured using established enzyme-linked immunosorbent assays. These parameters as well as fibrinogen and lipid values were statistically analyzed. Levels of sICAM-1, sVCAM-1, E-selectin, IL-6, IL-8, and MCP-1 were not significantly elevated in patients with SSHL. The clinical chemistry and hematologic determinations showed no significant differences between patients and control subjects. In spite of what the other researcher found, this study revealed no association concerning ISSHL and typical vascular risk factors such as lipids and fibrinogen. Soluble adhesion molecules were not elevated in the ISSHL group. The role of endothelial dysfunction represented by increased levels of soluble adhesion molecules in the pathogenesis of ISSHL remained unclear in the author's opinion.

The correlation between inflammatory biomarkers, stress, and the onset and prognosis of ISSHL was recently evaluated by Masuda and colleagues.[20] The authors enrolled 43 patients with ISSHL and found that, in ISSHL patients, neutrophils were above the reference range, natural killer cell activity (NKCA) was low and serum levels of IL-6 were high compared to controls. Neutrophil count correlated with the severity of hearing loss and the prognosis. The authors hypothesized that high neutrophils together with low NKCA and high IL-6 may induce the activation of nuclear factor B in the cochlea leading to ISSHL.

The role of genetic polymorphisms of inflammatory mediators in subjects affected by ISSHL has been recently investigated. Cadoni and colleagues[21] evaluated the role of proinflammatory genetic polymorphisms of the MCP-1 (CCL2), E-selectin, and *IL-6* gene, analyzing the frequency and distribution of selected single nucleotide polymorphisms in 87 ISSHL patients and 107 healthy controls. They found that the 174G/G polymorphism (with a wider distribution of wt/wt genotype in ISSHL patients than in the healthy controls) of the *IL-6* gene was significantly associated with the risk of ISSHL. Likewise Hiramatsu and colleagues[22] evaluated the associations of polymorphisms of several

inflammatory mediator genes in 72 patients affected by SSHL and 2010 adults (1010 men and 1000 women; mean age 59.2 years; range 40-79). Using multiple logistic regression they showed an odd ratio (OR) of 1.48 in subjects bearing IL-6 C-572G after adjustment for age, gender, and any history of hypertension, diabetes, or dyslipidemia.

Endothelial progenitor cells in sudden sensorineural hearing loss

In order to clarify the role of endothelial dysfunction in ISSHL, Quaranta and colleagues[23] have evaluated serum level of endothelial progenitors cells (EPCs). These cells, derived from bone marrow and first described by Ashahara and colleagues,[23,24] are a unique subtype of circulating cells with properties similar to those of embryonic angioblasts. These cells have the potential to proliferate and differentiate into mature endothelial cells.[24] The number of EPCs in healthy subjects is low and correlates with the low number of circulating vessel wall derived endothelial cells.[24] Several studies have shown that circulating EPCs are increased in case of acute vascular damage such as limb ischemia, acute myocardial infarction (MI) or vascular trauma, while are reduced in the presence of cardiovascular risk factors.[23,25,26]

Twenty-one patients affected by ISSHL were evaluated. Inclusion criteria for this study were as follows: hearing loss that appeared acutely and without recognizable cause; hearing loss of >30 dB hearing level affecting at least three contiguous frequencies, normal hearing in the contralateral ear, negative history of hearing loss or ear surgery in the affected ear and magnetic resonance imaging with gadolinium negative for VIII cranial nerve pathology. In addition, all patients taking statins were excluded, since these drugs influence the circulating levels of EPCs.[23,27] Blood samples were taken in the morning between 8 and 10 a.m. A full set of clinical chemistry, and hematological and hemostasis determination were obtained. For the purpose of the study only the results regarding vascular risk factors such as total and fractionated cholesterol (LDL and HDL), triglycerides, fibrinogen, and ESR were reported. The number of EPCs was analyzed by flow cytometry analysis of peripheral blood CD34+ KDR+ CD133+ cells. Circulating levels of EPCs were significantly lower in SSHL patients compared with controls. In particular, CD34+KDR+ cells and CD34+CD133+KDR+ cells were significantly reduced ($P<0.05$), supporting the hypothesis that this syndrome should be considered as a microcirculation disorder.

No significant correlations were found between EPCs levels with other risk factors, hearing level, and/or recovery rate. Thus, a reduced percentage of circulating EPCs in patients affected by ISSHL support the hypothesis that this syndrome should be considered as a microcirculation disorder and, in author's opinion, this should drive clinicians to implement all the traditional strategies used for preventing cardiovascular events, to also reduce the likelihood of ISSHL occurrence.[23]

Role of flow-mediated dilation, rheopheresis and peripheral endothelial dysfunction

Ballettshofer and colleagues,[28] in order to evaluate endothelial function in ISSHL patients, used a flow-mediated dilation (FMD) technique that consist in the induction of an enhanced flow in the proximal (brachial) artery by a post-ischemic (forearm) vasodilation with the consequence of a shear stress induced vasodilation. The technique has been shown to be a reliable and highly reproducible method[29] and is actually widely accepted as surrogate markers of early atherosclerosis.[30] The first finding of Ballettshofer's group pilot study was that patients suffering from unilateral ISSHL showed disturbed endothelial function in terms of disturbed flow associated (nitric oxide dependent) vasodilatation.[28] In view of the importance of nitric oxide for the regulation of regional blood flow,[31] this might contribute to reduce blood flow of the labyrinthine artery, supporting the hypothesis of a vascular pathogenesis of ISSHL. Potential modulation of systemic endothelial dysfunction by rheopheresis was examined by measuring flow-associated vasodilatation of the brachial artery (according to the criteria of the American College of Cardiology) in a small group of patients suffering from ISSHL (N=6.5 m/1f, mean age 56±11 years) within the last 3 days.[32] At baseline, five of the six patients with acute hearing loss showed endothelial dysfunction as evidenced by diminished flow-mediated vasodilatation (FMD<5%). After a single rheopheresis treatment, flow-mediated vasodilatation improved significantly (from 3.9±3.6% to 7.2±2.4%, $P=0.05$, mean ±SD, two-sided paired *T*-test). This was paralleled by a reduction in fibrinogen (364±216 mg/dL to 142±96 mg/dL, $P=0.03$), total cholesterol (228±23 to 98±10, $P<0.0001$) and LDL cholesterol levels (153±8 mg/dL to 83±23 mg/ dL, $P<0.01$). Based on this case series the authors concluded that single rheopheresis treatment might have an acute beneficial effect on endothelial dysfunction in patients suffering from ISSHL.[32]

Recently Ciccone and colleagues[33] have evaluated cardiovascular risk factors and endothelial function through FMD in subjects affected by ISSHL. Twenty-nine ISSHL patients and twenty-nine healthy controls underwent audiovestibular and clinical evaluation, carotid intima-media thickness (C-IMT) measurement and FMD measurement of the brachial artery (assessed as early markers of atherosclerosis). The results showed that FMD was significantly lower in the ISSHL patients than in the controls ($P<0.01$). Moreover, the total cholesterol and low-density lipoprotein cholesterol were significantly higher in the ISSHL patients than in the controls ($P<0.05$). The two groups did not differ with regards to C-IMT and other cardiovascular risk factors. Vestibular involvement was shown to be associated with lower FMD values ($P<0.05$). Finally, multiple logistic regressions highlighted the finding that only FMD values seemed to predispose individuals to developing ISSHL ($P=0.03$, OR=1.4). Based on these results the authors confirmed that ISSHL was associated with endothelial dysfunction and an increased cardiovascular risk, which supports the hypothesis of a vascular etiology for this disease.

Role of homocysteine and folate pathways

As widely known, homocysteine (HCY) is a non-protein amino acid, produced by the metabolism of methionine, which is introduced in the body through the diet. In the HCY metabolism a primary role is played by the 5-methylenetetrahydrofolate reductase (MTHFR), an enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate (methyleneTHF) to 5-methyltetrahydrofolate (methylTHF), which is essential for the transformation of potentially toxic HCY into methionine by 5-methyltetrahydrofolate-homocysteine methyltransferase.[34] High levels of HCY in the blood are now considered a major risk factor for developing cardiovascular disease (endothelial dysfunction, coronary atherosclerosis and MI), cerebrovascular disease (stroke) and peripheral vascular (arterial and venous thrombosis).[35]

In order to investigate the role of microcirculatory dysfunction in the etiology of ISSHL, Marcucci and colleagues[36] have evaluated 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 HCY; lipoprotein(a) [Lp(a)]; plasminogen activator inhibitor-1 (PAI-1)*] in addition to cardiovascular risk factors in patients with ISSHL. They investigated 155 patients (67 male/88 female; mean age: 55 (range 19-79 years) affected by ISSHL and 155 controls (67 male/88 female; mean age 54 (range 19-78 years). They found that 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]. No significant differences between patients and controls were observed for the other risk factors investigated. In their results independent risk factors for ISSHL at the multivariate analysis (adjusted for age, sex and the traditional cardiovascular risk factors) were the positivity of anticardiolipin: OR 5.6 [95% confidence interval (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. The authors concluded that, 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.[36]

Cadoni and colleagues comparing 43 patients with ISSHL and 24 controls found folate serum levels significantly lower in ISSHL (mean difference –1.96 ng/mL; 95% CI –3.31, –0.59 ng/mL; P=0.006) and reported a significant relationship between low folate levels and high HCY levels in all 43 patients (P<0.01). The potential influence of low folate levels on hearing impairment in ISSHL patients, according to the authors, could be explained by the effects on HCY metabolism and the diminution of folate antioxidant capacity.[37]

Fusconi and colleagues studied 49, 60, and 101 patients affected respectively by ISSHL, central retinal vein occlusion and stroke, and compared them with 210 healthy controls. They showed that the frequency of hyperhomocysteinemia (HCY ≥15 μmol/L) was higher in each disease group than in controls and a significant correlation between the MTHFR C677T mutation and hyperhomocysteinemia was found in all three diseases.[38,39] Uchida and colleagues[40] confirmed an association between the C677T polymorphism in the *MTHFR* gene and ISSHL comparing 33 cases of ISSHL to 2174 adults (1096 males and 1078 females) aged 40 to 79 years old. The authors in addition reported that the per-allele ORs for ISSHL risk were 1.687 (95% CI, 1.023-2.780) in model 1, with adjustment for age and sex, and 1.654 (CI, 1.003-2.728) in model 2, with adjustment for smoking status, body mass index, histories of heart disease, hypertension, and diabetes, in addition to the factors in model 1. In model 3, a significant association between ISSHL and the C677T polymorphism was observed under all genetic models independent of factors including folic acid and HCY, although there were only 25 cases and 1677 controls due to the addition of moderating factors. Lee and colleagues,[41] evaluating 33 ISSHL patients and 68 controls, could not find a statistically significant association between the *MTHFR C677T* gene mutation and ISSHL. The authors described only a significant difference between HCY, folate and cholesterol concentrations of ISSHL patients, compared with controls. High levels of HCY, a marker of vascular dysfunction, seems therefore to be associated with ISSHL; further researches are needed in order to clarify the role of polymorphisms of the *MTHFR* gene.

Idiopathic sudden sensorineural hearing loss and risk of thromboembolic events

Lin and colleagues,[42] using the Taiwan Longitudinal Health Insurance Database, compared patients diagnosed with ISSHL between January 1, 2001, and December 31, 2006, (N=44,830) with age-matched controls (1:1) (N=44,830). After a 3 years follow-up and after adjusting for potential confounds they described a higher risk of MI in ISSHL compared to controls (hazard ratio of 1.254, P<0.05). When stratified by patient age, the incidence of MI was 1.62-fold and 1.28-fold higher for ISSHL-diagnosed patients aged between 50 and 64 years and those aged ≥65 years (P=0.0064 and P=0.0001), respectively, than in the non-ISSHL group. The authors concluded that ISSHL may confer an independent risk of MI, and this observation may prompt the early detection and timely treatment of patients at a high risk of MI.

Other groups of authors have directed their studies toward the hypothesis of cochlear micro-thrombosis as a pathogenic mechanism of ISSHL, investigating the role of thrombophilia and cardiovascular risk factors.

Passamonti and colleagues[43] compared 118 patients with a first episode of ISSHL and 415 healthy controls and described that 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]. Capaccio and colleagues[44] evaluated prothrombotic gene mutations in patients with ISSHL subjecting 10 patients, who had previously experienced cardiovascular events, to hematologic tests (MTHFR C677T/A1298C, prothrombin G20210A, platelet GlyIIIaA1/A2, and V Leiden G1691A genotyping; fibrinogenemia; cholesterolemia: homocysteinemia; folatemia) and comparing the results with those of 100 previously investigated patients with ISSHL and of 200 healthy controls. They found that two patients had 2 mutant alleles, 6 had 3, and 2 had 4. The mean HCY, cholesterol, and fibrinogen levels were above the upper limit of normal and the mean folate levels were slightly above the lower limit of normal. So they concluded that the association between inherited and acquired prothrombotic factors in patients with ISSHL and thrombotic diseases in other sites suggests that a multifactorial mechanism may underlie microvascular cochlear impairment. Although ISSHL seems to be an independent risk factor for the development of a MI, more research is needed to clarify the role of acquired and congenital prothrombotic factors.

Discussion and Conclusions

The etiology of ISSHL is still unclear and there are still different hypothesis about risk factors for this condition.[45] The results of the present review support the hypothesis that endothelial dysfunction can be involved in the pathogenesis of ISSHL. There are several ways to assess the endothelial dysfunction, an early marker of atherosclerosis, in patients affected by ISSHL. As previously reported our group has demonstrated an increased expression of adhesion molecules, a reduced percentage of circulating endothelial progenitor cells and an altered FMD in ISSHL patients as early signs of endothelial damage.[17,23,33] We have therefore hypothesized that the endothelial dysfunction could predispose to the development of a pro-thrombotic state at the level of the inner ear and considering that the cochlear vascular tree is a terminal type, an interruption of vascular flow due to endothelial damage impairs cochlear functions.

Other factors may however impair cochlear microcirculation such as oxidative stress, inflammatory cytokines, HCY and genetically inherited prothrombotic state. The results of this review showed that in ISSHL patients, high levels of oxidative stress together with low levels of antioxidants have been reported as well as high levels of homysteine.

In conclusion, the high levels' findings of adhesion molecules, hyperhomocysteinemia and lower folate levels, unbalanced oxidative status, a lower value of FMD of brachial artery and a reduced percentage of circulating EPCs in patients affected by ISSHL, support the hypothesis that this syndrome should be considered as a microcirculation disorder based on endothelial dysfunction. These findings should drive clinicians to implement all the traditional strategies used for preventing cardiovascular events, to also reduce the likelihood of ISSHL occurrence. Moreover, these observations open the way to selective pharmacologic treatments able to correct the activation of endothelial cells.

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