Neurological Sciences (2019) 40:357–362
https://doi.org/10.1007/s10072-018-3647-0

ORIGINAL ARTICLE

MR evaluation of encephalic leukoaraiosis in sudden sensorineural hearing loss (SSNHL) patients

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Received: 16 March 2018 / Accepted: 13 November 2018 / Published online: 21 November 2018

Abstract

Epidemiological evidence suggests a strict correlation between sudden sensorineural hearing loss (SSNHL) and cerebrovascular disorders. Leukoaraiosis represents a diffuse alteration of the periventricular and subcortical white matter. The aim of our study was to verify if the presence of white matter hyperintensity (WMH) was higher in patients affected by SSNHL compared to controls and evaluate the correlation between WMH and the cardiovascular risk factors, hearing level, and the response to therapy in SSNHL patients. The study group included 36 subjects affected by unilateral SSNHL. Thirty-six age- and sex-matched normal subjects with a negative history of SSNHL were used as controls. All patients underwent magnetic resonance imaging (MRI) (1.5 Tesla GE Signa) and the extent of leukoaraiosis was assessed with the Fazekas scale. The results of the present study demonstrate a high prevalence of WMH in SSNHL patients compared to controls confirming the hypothesis of a vascular impairment in SSNHL patients. The higher recovery rate in patients with greater periventricular white matter hyperintensity (PWMH) may suggest a vascular etiology that is still responsive to medical treatment. We aim to expand both the number of patients and the controls to avoid the limitation of the still small number to warrant solid scientific conclusions.

Keywords Sudden sensorineural hearing loss · Leukoaraiosis · Small vessel disease · Magnetic · Resonance · Periventricular white matter lesions · PVWML · Recovery rate

Introduction

Sudden sensorineural hearing loss (SSNHL) [1] is defined as a sensorineural hearing loss characterized by a hearing loss of 30 dB or greater over at least three contiguous audiometric frequencies occurring within a 72-h period [2, 3]. The incidence of SSNHL is 5–20 per 100,000 [4–6]. Although individuals of all ages can be affected, the peak incidence is between the fifth and sixth decade of life. SSNHL occurs with equal incidence in men and women [4, 5, 7, 8]. Nearly all cases are unilateral; less than 2% of patients have bilateral involvement that is typically sequential [4, 5, 9]. Pathogenesis of this disorder is still not clear. Viral diseases, immune-mediated processes, and vascular injury have been proposed as pathogenic mechanisms [10]. Treatment of SSNHL is based on systemic steroids; other drugs such as rheological, thrombolytic, vasodilatory, and antioxidants have been also suggested [11]. Intratympanic steroids are used as a possible rescue therapy in non-responders [12]. Epidemiological evidence suggests a strict correlation between SSNHL and cerebrovascular disorders. In fact, patients affected by SSHL have a higher risk to develop cardiocerebrovascular disease [13, 14] while stroke patients have a 71% increased risk of SSNHL [15].

Leukoaraiosis [16] represents a diffuse alteration of the periventricular and subcortical white matter, correlated to the

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small vessel disease (SVD) and characterized by hyperintensity of the white matter hyperintensity (WMH) on magnetic resonance (MR) T2-weighted images or FLAIR sequences [17] (Fig. 1). The lesions have been initially considered "age-related spots," but several studies are now finding possible relations between leukoaraiosis and many other diseases [18, 19]. In a meta-analysis of 22 longitudinal studies, WMH was for example clearly associated with a threefold increased risk of stroke [20].

The aim of the present study was to verify whether the presence of WMH is more common in patients affected by SSHL, or not.

Furthermore, the correlation between WMH, cardiovascular risk factors, hearing level, and the response to therapy in SSNHL patients was also evaluated.

Materials and methods

The study group included 36 subjects affected by unilateral SSNHL, evaluated at the Otolaryngology Department of the University of Bari.

Inclusion criteria for this study were the following: sudden hearing loss of more than 30-dB hearing level (HL) affecting at least three contiguous frequencies, normal hearing on the contralateral ear, negative history of hearing loss or ear surgery in the affected ear, no VIII nerve pathology on MR images. All patients affected by Meniere's disease, herpes zoster oticus, noise-induced hearing loss, and other known causes of inner ear disease were excluded.

On the other hand, the control group included 36 patients—age and sex matched—with a negative history of SSNHL. A complete clinical history was obtained together with a standard audiovestibular investigation, consisting of pure-tone and speech audiometry, impedance audiometry, otoacoustic emissions, bithermal caloric testing of the vestibular function, vestibular evoked myogenic potentials, and MR imaging of the internal auditory canal and posterior cranial fossa.

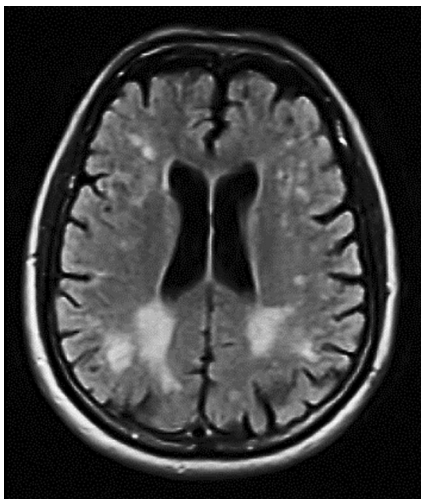

Fig. 1 MR exam: axial flair image. Leukoaraiosis: the white matter lesions look hyperintense signal

Pure-tone average (PTA) was obtained by averaging the air conduction thresholds at 0.25, 0.5, 1, 2, 3, 4, and 8 kHz.

Pure-tone and speech audiometry were tested every 48 h until hospital discharge.

PTA was used to define the severity of the HL: 20–40 dB indicated a mild HL, 40–70 dB a moderate one, 70–90 dB a severe one, and over 90 dB a profound one.

All patients were treated with the standard sudden deafness protocol including carbogen (95% CO_2 and 5% O_2) inhalation, vasodilators, and oral steroids (prednisone 1 mg/kg/die).

In order to evaluate hearing improvement, the following formula described by Shiraishi et al. (1993) was used [21]:

$$\text{Improvement rate}(\%) = \text{Initial PTA Final PTA}/\text{Initial PTA PTA opposite ear.}$$

Recovery was evaluated at hospital discharge, depending on the recovery rate (complete recovery: over 75%; good recovery: between 45 and 75%; slight recovery: between 20 and 45%; no recovery: under 20%).

All patients (cases and controls) underwent MRI (1.5 Tesla GE Signa) and the extent of leukoaraiosis was assessed with the Fazekas scale [22–24] by one expert neuroradiologist (compared to another blind neuroradiologist). Leukoaraiosis was classified in four stages according to presence, size, and confluence of white matter disease in the periventricular and deep white matter (PVWML) (DWML) (Table 1) (Fig. 2).

The data were imported into an Office Excel database and analyzed by Stata MP12 software. Continuous variables were expressed as mean ± standard deviation and range, while categorical variables as proportions. The Mann-Whitney *U* test (not parametric) was used to compare PVWML and DWML scores between SSNHL (group cases) and the control group; the exact Fisher test was used to compare categorical variables between groups. Finally, a multivariate linear regression model was constructed to identify a possible correlation between the periventricular and deep white matter hyperintensity

Table 1 Presence, size, and confluence of white matter disease in the periventricular and deep white matter

Periventricular white matter (PVWM) Hyperintensity	0	Absent
	1	"Caps" or pencil-thin lining
	2	Smooth "halo"
	3	Irregular PV signal extending into the deep white matter
Deep white matter (DWM) Hyperintensity	0	Absent
	1	Punctate foci
	2	Beginning confluence
	3	Large confluent areas

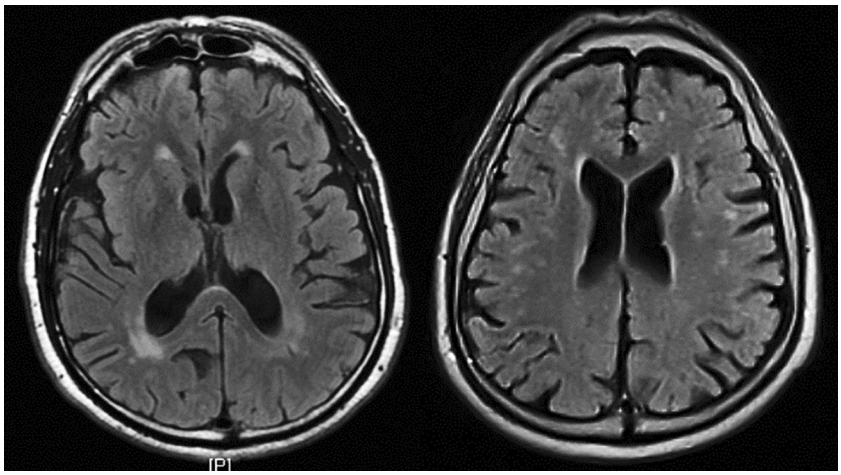

Fig. 2 MR exam: axial flair image. On the left, posterior periventricular hyperintensity (PVWM). On the right, deep white matter hyperintensity (DWM)

scores, and other parameters both clinical (age, gender, and BMI) and specialized (hematochemical and audiological parameters). The correlation coefficient (coef.) values were calculated with the 95% CI and were backed by *t* student. For all the tests used, a value of $p < 0.05$ was considered significant.

All the diagnostic procedures performed on patients respected the ethical standards of the institutional and/or national research committee, the 1964 Helsinki declaration, and all its later amendments or comparable ethical standards.

Results

The study sample (patients with SSNHL) included 36 subjects, 20 males (55.6%), and 16 females (44.4%); the mean age of the sample was 54.4 ± 15.6 years (range, 39.2–77.0).

The control group consisted of 36 healthy subjects (20 females and 16 males), with a mean age of 53.0 ± 12.5 years, (range, 33.0–71.0) who underwent MRI for headache and dizziness.

The analysis of MRI T2 FLAIR images showed significantly higher WMH values in patients with SSHL than in the control group (Table 2).

Figure 3 describes the distribution of the variable "PVWM" according to the Fazekas scale in the two different groups (case/control); a statistically significant difference in the distribution of the proportions in the two groups was detected ($\chi^2 = 13.9$; $p = 0.002$) (Fig. 3).

Table 2 WMH values in patients with SSHL in the control group

Variable	Case group	Control group	*z*	*p*
PVWM	1.1 ± 1.0 (0.0–3.0)	0.4 ± 0.5 (0.0–2.0)	3.3	0.001
DWM	0.8 ± 0.9 (0.0–3.0)	0.3 ± 0.5 (0.0–2.0)	2.3	0.019

Figure 4 describes the distribution of the variable "DWM" according to the Fazekas scale in the two different groups (case/control); a statistically significant difference in the distribution of the proportions in the two groups was detected ($\chi^2 = 7.9$; $p = 0.030$) (Fig. 4).

A significant difference in the two groups is observed regarding the PVWM variable (66.7% of cases compared to 36.1% of controls) and the DWM variable (50% of cases compared to 27.8% of controls).

PVWM lesions were absent in the 33.3% of the examined cases, while DWM in the 50%.

On the other hand, PVWM lesions could not be detected in the 63.9% of the controls, while DWM in the 72.2%. By using a linear multivariate regression analysis, PVWMH value correlated with age (coef. = 0.05; $p = 0.006$), gender (coef. = − 0,9; $p = 0.043$), BMI (coef. = 5.2; $p = 0.010$), cholesterol levels (coef. = 0.01; $p = 0040$), ESR (coef. = − 0.5; $p = 0.042$), and recovery rate (coef. = 0.02; $p = 0.011$) (Table 3). No statistically significant differences in the distribution by gender are observed ($\chi^2 = 1.5$; $p = 0.730$). DWMLs did not correlate with any of the previous variables ($p > 0.05$).

Discussions and conclusions

To date, little is known about the pathogenesis of SSNHL, but most probably it should be described as a multifactorial syndrome rather than as a simple disease [25].

Epidemiological evidence suggests a strict correlation between SSNHL and cerebrovascular disorders [13, 14], as well as clinical and experimental studies have suggested an endothelial impairment in patients affected by SSNHL. In fact, high levels of adhesion molecules, hyperhomocysteinemia, low folate levels, unbalanced oxidative status, low value of flow-mediated dilatation (FMD) of the brachial artery, and a reduced percentage of circulating endothelial progenitor cells have been described in patients affected by SSNHL [26].

The current limit of our study is related to the small number of patients and controls, which can influence the multivariate analyses.

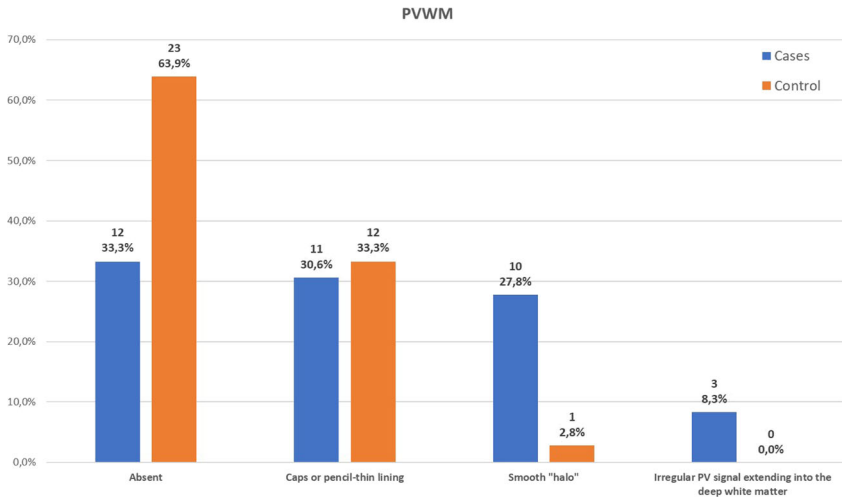

Fig. 3 The distribution of the variable "PVWM" according to the Fazekas scale; $\chi^2 = 13.9$; $p = 0.002$

However, the results of the present study demonstrate a high prevalence of WMH in SSNHL patients compared to controls, confirming the hypothesis of a vascular impairment in SSHL patients.

Until recently, leukoaraiosis has been considered the inevitable consequence of normal aging [27], although several studies have demonstrated that WMH is clearly associated with neurological disorders, such as progressive cognitive impairment, dementia, and stroke [20]. The prevalence of WMH has been shown to increase with age, along with vascular risk factors, including hypertension, diabetes, and smoking [27].

Chronic hearing loss [28], abnormal gait, and disturbed balance have also been reported in patients with WMH [29–31]. Post-mortem studies have been used to assess the pathogenesis of WMH and have demonstrated heterogeneous brain damage, ranging from slight disentanglement of the matrix to varying degrees of myelin and axonal loss. In addition, changes such as lipohyalinosis, arteriosclerosis, vessel wall leakage, and collagen deposition in venular walls have been described [32].

Ischemia/hypoxia and hypoperfusion due to altered cerebrovascular autoregulation, blood-brain barrier leakage, inflammation, degeneration, and amyloid angiopathy have been proposed as pathogenetic mechanisms of WMH [27]. The clinical association between SSHL and WMH has never been reported in adults affected by SSHL.

However, Uchida et al. [33] in 2011 evaluated the contribution of protein kinase C-eta 1425G/A polymorphism (a gene associated with cerebral infarction and hemorrhage) and WMH in patients affected by SSHL; this demonstrated an association of the 1425G/A polymorphism with SSHL only in the presence of a high level of leukoaraiosis.

On the other hand, Hiramatsu et al. (2012) investigated the associations between inflammatory mediator gene polymorphisms and susceptibility to SSNHL, supporting the hypothesis that inflammation is associated with increased permeability of blood vessels and therefore WMH. The authors therefore showed that the IL-6 C-572G polymorphism was associated with a risk of SSNHL and that, since permeability of blood vessels in the inner ear is frequently increased in patients with SSNHL, inflammation of the inner ear might be involved.

Statistical analysis showed that in SSHL patients, PVWMH correlated with age, female sex, BMI, cholesterol levels, and recovery rate. PVWMH and DWMH were initially described as two different entities [32], but recent evidence

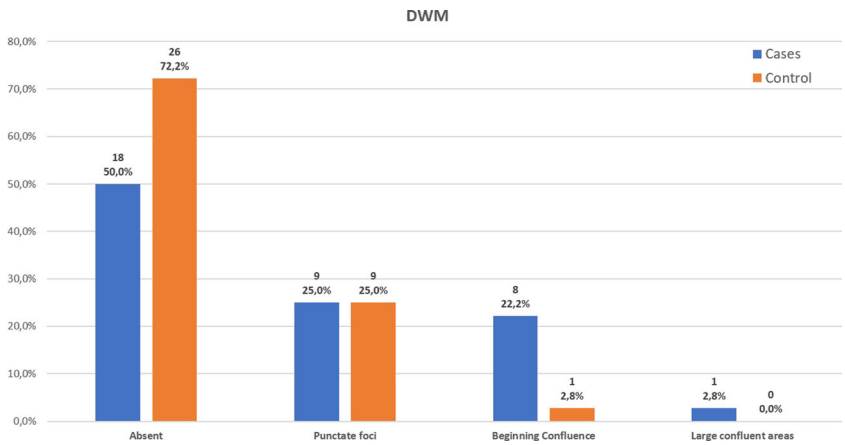

Fig. 4 The distribution of the variable "DWM"; $\chi^2 = 7.9$; $p = 0.030$

Table 3 Analysis of the determinants of PWML score in a multivariate linear regression model

Variable	Coef.	95% CI	t	p
Age (years)	0.05	0.02 to 0.08	3.3	*0.006*
Gender (male/female)	− 0.9	− 1.9 to − 0.1	2.2	*0.043*
BMI	5.2	1.5 to 8.9	3.0	*0.010*
Hypertension (Y/N)	− 0.6	− 1.5 to 0.4	1.2	0.225
Smoke (Y/N)	0.2	− 0.6 to 1.0	0.4	0.689
Glycemia	108.5	− 105.2 to 322.5	1.1	0.293
Cholesterol	0.01	0.01 to 0.03	2.3	*0.040*
Triglycerides	− 0.1	− 0.7 to 0.7	0.0	0.986
Fibrinogen	− 1.9	− 5.6 to 1.8	1.1	0.293
PT	2.4	− 3.6 to 8.5	0.9	0.402
HCT	− 0.1	− 0.1 to 0.1	0.6	0.568
platelet count	0.1	− 0.1 to 0.1	1.6	0.143
VES	− 0.5	− 0.9 to − 0.1	2.3	*0.042*
Pathological PCR (Y/N)	0.9	− 0.7 to 2.5	1.3	0.232
Cardiovascular risk (Y/N)	0.5	− 0.7 to 2.5	0.7	0.497
Total PTA	0.1	− 0.1 to 0.2	0.3	0.804
Low-frequency PTA	− 0.1	− 0.1 to 0.1	0.6	0.556
High-frequency PTA	0.1	− 0.1 to 0.1	0.1	0.935
Recovery rate	0.02	0.01 to 0.03	3	*0.011*

[34] suggest that DWMH develops in case of more severe tissue damages (vacuolation and increased tissue loss).

In particular, PWMH is thought to be caused more likely by regional hemodynamic alterations (e.g., impaired fluid reabsorption) rather than by ischemic disorders; this explains why PWMH is liable to modifications after therapy while deep lesions are not since they are more easily encountered in small-vessel ischemic cerebropathy—SVD [35]. The higher recovery rate in patients with greater PVWMH may suggest a vascular etiology, leading to a possible response to medical treatment; on the other hand, no correlation was found regarding DWMH.

Conclusions

The present data show the importance of the identification of WMH in SSHL, in order to select patients that are at risk of developing cerebrovascular complications and to establish proper therapies and a healthier lifestyle. Therefore, in these patients, MRI should be used not only to exclude a VIII nerve pathology, but also to assess the presence of brain lesions such as leukoaraiosis. We aim to expand the number of both patients and controls to avoid the limitation of the still small number and therefore to bring solid scientific conclusions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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