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Prognostic Value of Early Magnetic Resonance Imaging Patterns In Sudden Hearing Loss

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Abstract

Introduction. Sudden Sensorineural Hearing Loss (SSHL) is a relatively frequent disease, but a sensitive marker or a reliable test to identify the underlying cause is still unavailable. Neuroradiology appears to offer the most promising tools, especially Magnetic Resonance Imaging (MRI). In the most recent study from our group, we explored the possibility to detect subtle changes in the inner ear compartments at MRI, by means of a 3D-fluid-attenuated inversion recovery (FLAIR) sequence, aiming to identify 3 distinct MRI patterns [hemorrhagic, inflammatory, brain-labyrinth barrier (BLB) breakdown]. In the present study, we contrasted the MRI patterns at onset with relevant prognostic factors, with the audiological features of each patient's SSHL and with treatment outcomes.

Methods. In this prospective study, we enrolled 50 adult subjects (54,61 ± 18,26 years) with SSHL. They underwent an MRI within 72 hours from admission, and 5 audiological evaluations: at admission, on the 5th day after the start of medical therapy, at the end of the first cycle of hyperbaric oxygen (HBO) therapy, and 1 and 6 month later.

Results. Positive MRI (MRI+) findings generically correlated with worse audiological outcomes at 1 month, but the different MRI patterns were not correlated with any specific prognostic model, despite rigid protocol settings. However, a significant difference was found for low-tones SSHL, which were always negative at MRI, and for profound SSHL which demonstrated an MRI+ in 80%. ($p<0.0125$)
At the onset of SSHL, MRI+ was found in 29/50 cases (58.0%) and was related with lesser degree of recovery of pure-tone average (PTA) at 1 month and lesser chance to retain the hearing threshold benefit in the long term. Given the limited numbers of patients enrolled so far, the relative impact of comorbidities on each MRI pattern remains uncertain. At 6 months, we observed a trend of greater and more stable recovery ($p=0.023$), and less frequent recurrence of SSHL in MRI- patients.

Conclusions. the 3 observed MRI patterns did not correlate consistently with specific audio-vestibular features or any peculiar aspect of the patient's clinical history. Larger series of patients with SSHL are needed, possibly from multicentric studies.

Introduction

Sudden Sensorineural Hearing Loss (SSHL) is a relatively frequent disease, with a prevalence ranging between 5 and 27 per 100,000 inhabitants on an annual basis (Chandrasekhar et al., 2019).

It is defined as a loss of hearing of the sensorineural type of at least 30 dB HL across 3 contiguous frequencies, occurring rapidly (within 24h) with or without associated vestibular disfunction, tinnitus and/or ear fullness.

Several causative factors have been suggested (Ciorba et al., 2016; Li et al., 2018), but a sensitive marker of the disease or any single reliable test to identify the underlying cause is still unavailable. Therefore, many different empirical treatment protocols have been implemented (Coelho et al. 2011; Plontke, 2017; Marx et al. 2018), none of which has proven superior to the others. The lack of etiological identification and the incapacity to assess the extension of cochlear damage explain our inability to foresee the chance and degree of recovery and the risk of relapse. (Cassandro, 2019).

In 2008, O'Malley stated that SSHL is a medical emergency in search of appropriate diagnostic techniques and treatments. Twelve years after that statement, we are still in search of the "diagnostic wand"

Neuroradiology appears to offer the most promising tools and, according to the recommendations of the updated Clinical Practice Guidelines of the AAOO (Chandraskhar et al 2019), [quote] "*Clinicians should evaluate patients with SSHL for retrocochlear pathology by obtaining magnetic resonance imaging (MRI)"*

Nowadays, advancements in MRI not only allow to detect retrocochlear pathologies, but it have provided the means to study the inner ear compartments in more detail (Sugiura et al., 2006; Berrettini et al. 2013; Conte et al 2017; Inui et al. 2020).

In the most recent study from our group (Conte et al.,2019), we explored the possibility to detect subtle changes in the inner ear compartments of the affected side by means of an MRI obtained within 72 hours from patients' admission and repeated 4-hours after i.v. Gadolinium administration, using a 3D-fluid-attenuated inversion recovery (FLAIR) sequence. We were able to identify 3 distinct MRI patterns [hemorrhagic, inflammatory, brain-labyrinth barrier (BLB) breakdown] but could only ascertain a non-specific correlation, although statistically significant, between "positive" MRI patients and an unfavorable outcome.

In the present study, we expanded the analysis by contrasting the MRI patterns at onset with some of the most relevant prognostic factors (Passamonti et al., 2015), with the audiological features of each patient's SSHL and with the outcomes of treatment.

Materials and Methods

Study Population

In this prospective study, we enrolled 50 consecutive adult patients with SSHL, admitted at the Emergency Ward of Fondazione IRCCS Ca` Granda—Ospedale Maggiore Policlinico of Milano (Italy), who had undergone MRI within 72 hours from admission. (see specific section for MRI protocol)

All sequential patients accessing the Emergency ward of the Hospital for a sudden deafness between June 2016 and December 2019 initially received an Otorhinolaryngological consultation by ENT Specialists and were then referred to the Audiology Unit. Then, they underwent a complete audiological evaluation, a blood sample for testing the blood clotting and immunological profile, and a serological search for viral agents including Epstein-Barr (EBV), Cytomegalovirus (CMV) and Varicella-Zoster Virus (VZV). A pharmacological treatment was immediately implemented after admission (see details in following section)

Follow-up consisted in an Audiological evaluation performed on the 5th day after the start of medical therapy; it was repeated at the end of the first cycle of hyperbaric oxygen (HBO) therapy (consisting in 8 daily consecutive sessions) and at 1 month after the onset of audiological symptoms. Informed consent was obtained from all patients after the initial detailed interview and counselling.

Of the 50 included patients, 24 were males and 26 females; the mean age was 54,61 ± 18,26 years (range: 19-90). Diagnosis of SSHL was defined according to the guidelines of the American Academy of Otolaryngology (AAO-HNS): a sudden sensorineural hearing loss of 30 dB HL or more over at least three contiguous audiometric frequencies, developing over a period up to 72 hours without evident causes.

Exclusion criteria were age <14 years, previous episodes of ipsilateral SSHL, known middle or inner ear diseases, previous otologic surgery, peri-lymphatic fistula, ototoxic drugs (including chronic anti-inflammatory therapy), neurological diseases with hearing involvement, acoustic trauma, family history of genetic deafness, kidney insufficiency, and pregnancy.

Audiological Evaluation

For each patient a detailed clinical history was collected, focused on the precise course of the SSHL (date of onset, possible triggering factors, variations in subjective symptoms over time), and of associated audiological (tinnitus, hyperacusis), vestibular (rotatory vertigo, dizziness, unsteadiness and gait instability) and non-otological symptoms (headache, paresthesia, neck stiffness, other neurological). Comorbidities where thoroughly recorded, as well as any pharmacological treatment.

After otomicroscopy, the following audiological test were performed:

1. pure-tone threshold audiometry at 0.25-0.5-1-2-4-8 kHz by air conduction (AC) and 0.25-0.5-1-2-4 kHz by bone conduction (Amplaid A321 Twin Channel audiometer (Resonance, Gazzaniga, Italy), with Sennheiser HAD 200 earphones in a soundproof booth (ANSI S3.6-2018; ANSI S3.21-1999);
2. tympanometry at 226 Hz; recording of ipsi- and contra-lateral acoustic reflexes elicited at 0.5-1-2-4 kHz (Clarinet, Inventis Biomedica, Padova, Italy);
3. recording of ipsi- and contralateral distortion product otoacoustic emissions (DPOAE) (ILO V6 Clinical OAE Software, Otodynamics Ltd, Hatfield Hearts, UK) elicited at 1-1,5-2-3-4-6-8 kHz they were considered present in case of response greater than 0 dB SPL in at least four of the seven tested frequencies (29);
4. speech audiometry consisted in a recognition task with 20 lists of 10 disyllabic words phonetically balanced for the Italian language (30) delivered via TDH-39 ear muffs (Amplaid, Gazzaniga, Italy); a words recognition score (WRS) was assessed for each presentation level (dB HL), and an intelligibility curve was derived;
5. a bedside vestibular evaluation;
6. Video Head Impulse Test (vHIT) by the ICS Impulse device and OTOsuite Vestibular software (GN Otometrics, Taastrup, Denmark). It consists in the recording of vestibulo-ocular reflex (VOR) response to 20 high-frequency head movements in the 3 semicircular canal planes that are plotted on an X-Y graph and analyzed for the reactive eye movements (compensatory saccades). Overt and covert saccades are detected and recorded. Normal gain values range between 0.80 and 1.00.

The pure-tone average (PTA) was calculated as the mean value of AC thresholds at 0.5-1-2-4 kHz; the degree of hearing loss was defined according to the ASHA guidelines (31).

At the time of diagnosis, audiogram shapes were divided in ‘‘low-tones SSHL’’ (average of 125, 250, and 500 Hz were ≥ 30 dB HL and worse than 2-4-8 kHz average), ‘high-tones SSHL’’ (2-4-8 kHz average were ≥ 30 dB HL and worse than 125-250-500 Hz), ‘‘flat curves’’ (less than 20 dB HL difference between the highest and the lowest threshold), and ‘‘profound SSHL’’ (thresholds >90 dB HL on all tested frequencies). (Watanabe and Suzuki 2018) An “audiological improvement” was defined as a post-treatment amelioration of the PTA > 15 dB HL across 3 adjacent frequencies at 1 and 6 months. (Siegel et al 1975) At the end of the therapeutic path all patients were enrolled in yearly follow-up and instructed to urgently access the outpatient clinic in case of recurrence (as in standard clinical practice): all patients were screened for recurrence up to 48 months after the 1st episode.

Imaging Acquisition and Analysis

MR images were acquired on a 3-Tesla Scanner (Achieva, Philips Healthcare; Eindhoven, The Netherlands) using a 32-element phased array head coil. The MRI protocol is the same reported by Conte et al. 2019. The symmetry of MRI signal of inner ear structures on pre-contrast T1-weighted and 3D-FLAIR sequences, and

the symmetry of contrast-enhancement on postcontrast 3D FLAIR or 4 hour-delayed 3D-FLAIR sequence was checked. In case of MR signal and/or contrast-enhancement asymmetry, MRI examination was defined as "positive", alias pathological, (MRI+) and the ear with higher signal and/or contrast-enhancement was considered as affected.

As shown in Figure 1, three different radiologic patterns were identified by combining the analysis of T1 and FLAIR sequences, based on the findings of previous studies (Berrettini S. et al 2013, Conte et al 2017, Conte et al 2018, Conte et al 2019):

- *pattern 1*: high-intensity signal in the T1-weighted sequence, due to the presence of intra- and extra-cellular methemoglobin, and in 3D-FLAIR images, due to the increased protein content in the inner ear fluids, secondary to the presence of methemoglobin. This pattern is consistent with intracochlear hemorrhage;
- *pattern 2*: negative T1 sequences and high-intensity signal in 3D-FLAIR images, due to the presence of a proteinaceous exudate in the inner ear fluids, potentially indicating an acute inflammatory process;
- *pattern 3*: negative T1 and FLAIR images but postcontrast enhancement (after i.v. gadolinium injection), due to isolated brain-labyrinth-barrier (BLB) breakdown.

Medical Management

The therapeutic protocol was the same for all patients included in the study. In agreement with the Clinical Practice Guidelines of the AAOO (Chandraskhar et al 2019), it consisted of:

1. an immediate administration of oral steroids: Prednisone 25 mg b.i.d. for 5 days followed by a half-dose tapering every 4 days for a global treatment duration of 13 days.
2. intratympanic steroid (salvage therapy): reserved to patients with initial PTA threshold worse than 60 dBHL who did not show any audiometric evidence of recovery at day 5th of oral therapy. It consisted of Dexamethasone 4 mg/ml, administered through a trans-tympanic injection into the middle ear under contact anesthesia of the eardrum, repeated every other day for a total of three sessions.
3. Independent of the hearing threshold, Hyperbaric Oxygen Therapy (HBO), was always started as early as possible, concomitant to oral steroids. In case of intratympanic treatment, it was suspended for 48hs after each injection. Each patient received 1 to 3 cycles of 8 consecutive 90-minute session in a sealed chamber at 2,5 BAR (ILMI, Istituto Lombardo di Medicina Iperbarica). After each cycle (8 sessions) a pure tone audiometry was obtained, and the treatment was suspended only in case of complete hearing recovery.

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (IRB and Ethical Committee of Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy, identification number: 616, June 19, 2019: 473_2018) and with the Helsinki Declaration of 1975, as revised in 2008.

Statistical analysis

Continuous variables are expressed as median ± interquartile range; qualitative variables are expressed as absolute frequency and percentage. Comparisons among groups were carried out with $\chi 2$ test for nominal variable, when comparing multiple variables, as in risk factors analysis we applied Bonferroni correction, Wilcoxon signed-rank test was used for continuous repeated measures and variables between two groups, Kruskal-Wallis test for comparison between more than two groups. Chi-square or Fisher's exact test was used for categorical variables.

Data were analyzed using IBM SPSS 25 System (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY). Differences were considered statistically significant if the "p" value was less than 0.05.

Results

All patients were affected unilaterally: 25 in the right (50%) and 25 in the left ear (50%). The mean PTA at initial examination was 69.39 ± 29.07 dB HL, while PTA at 1 month after the start of treatment had improved at 48.82 ± 31.57dB HL. The distribution of the degree of hearing loss was mild to moderate (including low-tones SSHL) in 28 subjects, severe in 12 and profound in 10.

The mean delay between onset of SSHL and the start of therapy was 7.84 ± 9.50 days. The mean delay between onset of SSHL and MRI was 10.95 + 9.52 days (depending on referral delay). As already stated in the methods section, the MRI was always obtained within 72 hours from admission.

DPOAEs recorded at admission were present only in 6 out of 50 patients (12.0%) with milder degrees of SSHL. At the 1-month follow-up they re-emerged in 28 out of the 48 tested (58.3%). vHIT data obtained in 38 patients showed normal responses from the semicircular canals; in 4 patients (8%), a reduced response from the ipsilateral labyrinth was assessed. The vHIT was repeated at the 1-month visit in 37 out of the 38 patients, showing normal labyrinthine response in all cases.

MRI imaging was positive in 29/50 cases (58.0%). The distribution of the audiometric profiles at admission according to the MRI findings is reported in Table I.

A significant difference was found for low-tones SSHL (p=0.003), which were always associated with MRI-, and for profound SSHL which demonstrated MRI+ in 80%.

As far as the high-tones SSHL and the flat curves, no statistically significant differences between MRI+ and MRI- patients were observed. (Fisher exact Test p=0.20)

At admission, 21 out of 50 patients (42%) had vertigo at onset whom 4 patients with vertigo showed MRI- (8%) while 17 had MRI+ (34%).

Table II summarizes the audio-vestibular features of the sample population, comparing the MRI+ with the MRI- patients.

The detection of MRI+ at the onset of SSHL was related with lesser degree of recovery of PTA at 1 month (63.75 vs 21.25 dB HL) and lesser chance to retain the hearing threshold benefit in the long term .(34.5% vs 71.4%) Unfortunately, poorer mean hearing thresholds at admission (PTA of 67.25 vs 57.5 dB HL) and greater likelihood of associated vestibular test abnormalities (75.8% vs 41.6%) did not reach a statistical significance. The presence of ipsi- and contralateral DPOAEs did not appear to play any prognostic role.

Among the 29 positive (MRI+) cases, 5 showed a type 1 pattern (17.2%), 16 a type 2 pattern (55.2%), and 8 a type 3 pattern (27.6%). (Fig. 2)

The initial audiological contour was not associated with any specific MRI pattern, except for profound SSHL that were associated with pattern 1 (“hemorrhagic”) in 5 out of 8 cases. Three other cases showed pattern 2 (“inflammatory”) and 2 had MRI-. The differences were not significant. (p>0.05, Chi-Square)

Moderate/severe flat audiometric curves (n=9) showed pattern 2 (“inflammatory”, n=3), pattern 3 (“BLB breakdown”, n=2) or MRI- (n=4). Among the 25 patients with moderate to severe high-tones SSHL, 9 (36%) resulted negative at MRI, while 10 patients were classified as pattern 2 (“inflammatory”), and 6 patients as pattern 3 (“BLB breakdown”).

When contrasting the MRI+ findings with the presence of comorbidities, we were unable to demonstrate any statistically significant correlation, as summarized in Table III. The relative impact of comorbidities on each MRI pattern remains unknown, given the paucity of patients in each subgroup, insufficient for a statistical analysis.

The audiometric outcomes of treatment in the different subgroups of SSHL patients according to the MRI findings are shown in Figure 3.

The differences of recovery rate between either MRI+ and MRI- patients or among the different MRI patterns did not reach statistical significance, despite milder hearing loss were more frequently MRI- and showed a trend toward a larger degree of improvement. Similarly, the observed MRI patterns showed no statistically significant differences in terms of chance of recovery. (PHI = 0.253)

The degree of recovery at 1 month after treatment was slightly better in the MRI- patients, who started also with better pre-treatment audiograms, on average, than MRI+ patients: 61.6 vs 74.4 dB HL (Table I). Similarly, in the long run we observed a non-significant trend of greater and more stable recovery, together with a less frequent recurrence of SSHL in MRI- patients.

A multinomial regression analysis on the MRI+ patients comparing the MRI pattern with either the pathological vHIT or the ipsi- or contralateral absence of DPOAE failed to assess any significant correlation.

Noteworthy, however, 3 out of the 6 patients with a low-tones SSHL at admission (50%) developed vertigo attacks later on, and were diagnosed as definite Meniére disease (MD), despite an initially MRI-. Of these 6 patients with a low-tone SSHL at admission, none had vertigo at onset but all of them had relapse of the auditory symptoms at follow-up.

Discussion

In the 2019 update of the practice guidelines of the AAO-HNS (Chandrasekhar et al 2019), the panel of experts reached a consensus on the recommendation to request an MRI in every case of sudden deafness, despite limited cost-effectiveness evidence (Marhous et al, 2008; Hojiat et al., 2017 ; Lee et al., 2018). The purpose is to rule out a possible retrocochlear disease. Actually, vestibular schwannoma has been detected in up to 4.7% of patients admitted for SSHL by conventional MRI (Chau et al., 2010; Maggie Kuhn 2011). Conversely, the diagnostic workup for hearing loss of cochlear origin, including SSHL, has always lacked an adequate morphological support from imaging.

Over the last years, different groups tried to address the limitations of MRI in studying the inner ear by modifying the existing MRI protocols (Attye et al. 2015; Triulzi et al 2019).

The advent of 3-Tesla MRI devices combined with new sequences such as 3D-FLAIR or 3D-FIESTA (Touska and Connor 2019; Eliezer et al., 2019) allowed to obtain more detailed anatomical information on the inner ear structures and their content; in synergy with contrast enhancement evaluation and 4-hours delayed acquisitions, they led to a more precise definition of the fluid compartments as well as of the damage site and extension, becoming the most reliable morphological indicator of endolymphatic hydrops. (Conte et al. 2018–1; Conte et al., 2018-2; Lopez-Escamez and Attye, 2019).

Berrettini et al (2013). first reported three distinct MRI signal patterns in SSHL: the first pattern was composed of T1 hyperintensity and FLAIR hyperintensity within the membranous labyrinth thought being methemoglobin from hemorrhage. The second pattern featured high intensity on FLAIR without concurrent hyperintensity on T1, which was believed to represent proteinaceous exudate, likely due to an acute inflammatory process, without hemorrhage. The third pattern was defined by intense contrast enhancement, indicating the breakdown of the BLB and a high protein content within the fluid. Since then, different researchers confirmed the evidence of some recurring typical imaging patterns, similar to those described in this paper; MRI findings suggestive of hemorrhage or inflammation or BLB breakdown have been separately described by different authors (Lee et al 2012; Byun et al. 2019, Conte et al 2019), accounting for 25.8 - 64.5% of SSHL patients

In our previous study (Conte et al., 2019), we described the most frequent patterns observed at MRI 4-hours after i.v. Gadolinium administration, using a 3D fluid attenuated inversion recovery (FLAIR) sequence. The sensitivity of this MRI protocol in detecting subtle changes in the affected inner ear was high (Cohen K = 1 confronting clinical examinations and MRI); the correlation with unfavorable outcome in “positive” MRI patients allowed us to propose this technique as a promising diagnostic tool.

Different etio-pathogenic mechanisms may underly the 3 MRI patterns that have been identified:

In pattern 1, the high-intensity signal observed in the T1-weighted sequence and in 3D-FLAIR images, is due to the presence methemoglobin. Methemoglobin is a by-product of red cells disaggregation (Farahani, Keyvan, et al 1999) and it accumulates in the intra- and extra-cellular spaces as a result of intracochlear hemorrhage

(Vivas et al., 2018; Tanigawa et al 2010); it is also responsible for the increased protein content in the inner ear fluids, that is easily recognized as high signal.in 3D FLAIR MRI sequences (Berrettini et al 2013, Sugiura et al. 2006)

In pattern 2, the normal intensity of the signal in T1 sequences and its intensification in 3D-FLAIR images can be explained by the presence of a proteinaceous exudate in the inner ear fluids. It has been related with the filtration of proteins in the extravasal spaces of the inner ear during an acute inflammatory process (Sugiura et al. 2006)

In pattern 3, both T1 and FLAIR sequences appear initially negative. The characteristic post-contrast enhancement (after i.v. gadolinium injection), has been attributed to isolated BLB breakdown. This hypothesis is supported by many research groups. (Mark et al 1992, Pyykkö et al. 2010)

Recently, Inui et al (2020) utilized an MRI-based volumetric analysis of inner ear fluids in order to differentiate SSHL from fluctuating cochlear hearing loss; they considered it a reliable predictor of fluctuating episodes, although they observed a vast heterogeneity of patterns and degrees of abnormalities.

The main accepted treatment of SSHL is based on steroids, either administered systemically or via the intratympanic route. Unfortunately, the results of a few metanalysis (Conlin and Parnes 2007, Labus et al. 2010, Lin et al 2012) revealed no compelling evidence of benefit of steroids (either in combination with antivirals or not) over placebo or over any other active treatment. All outcomes studies for SSHL are loaded with the variability of the individual treatment. For the purposes of this study, all our patients were treated with the same protocol, consisting in oral prednisolone and HBO, with the addition of intratympanic dexamethasone in the more severe and resistant cases. Thus, the variables impacting on the outcomes were reduced, and we focused the analysis on the correlation between the different MRI patterns observed at the onset of SSHL and the clinical history, the audio-vestibular picture and the outcomes of treatment.

In the present study, the overall recovery rate for the whole group of SSHL patients was 46,0%, somewhat lower than in the majority of the comparable outcome studies in the literature. It might be explained by the high rate of severe to profound SNHL (n=22/50 patients) or by the prevalent audiogram shapes (high-tones SSHL or profound SSHL: n= 35/50) usually considered prone to poorer outcomes (Oishi, Naoki, et al. 2010).

MRI patterns vs audio-vestibular features

Theoretically, we would expect a greater chance of recovery in SSHL with an underlying inflammatory etiological substrate, as identified by MR pattern 2, vs. the hemorrhagic (pattern 1) or BLB breakdown (pattern 3), given the different pathogenesis in the 3 instances, (Lee et al 2016) and the mainly anti-inflammatory action of the steroid therapy. Instead, in the current study we were unable to highlight significant differences in the outcomes between the different MRI patterns: the mean hearing gain in pattern 1 was 3.75+13.22 dB HL, in

pattern 2 it was 18.5+24.6 dB HL, in Pattern 3 12.2+13.9 dB HL. On a purely speculative ground, we might argue that with the spatial resolution of current 3T MR imaging systems, the "positive" MRI images (taken on an average of 10 days after the onset of SSHL) reflect already extensive damages to the cochlea, and, whatever the etiology, they end up with similar recovery trends. Deeper insights could emerge from the use of stronger magnetic fields (7T, 9T), or from earlier examinations (within 24-48 hours from the onset of SSHL), which is difficult to accomplish.

A second negative observation is the absence of links between the shape of the audiogram and the MRI patterns. Our data suggest that no specific audiogram profile correlates with MRI+ vs MRI- patients. All 3 MRI patterns were observed in patients with low-tones SSHL, high-tones SSHL or flat audiometric curves, and the differences in distribution were not significant.

However, MRI+ findings were related with more severe degrees of hearing loss (n= 14 with severe to profound SNHL in the MRI+ group vs n= 8 in the MRI- group), and the latter was directly linked to a greater extent of anatomical alterations of the cochlea and of the vestibular structures (Mark and Fitzgerald 1993; Lammers et al. 2019) The only exception was the low-tones SSHL, which was always correlated with MRI-. We can speculate that these patients might be a peculiar sub-group of SSHL that represent the initial stage of Meniere's disease. Actually, 3 out of 6 patients with the up-sloping audiometric contour and a MRI-, manifested clear MD symptoms during the follow-up. This has been reported also by Inui et al. (2020), although with a different MRI protocol.

In our study, a MRI+ was related not only to a worse hearing threshold at onset but also to a worse PTA at 1 month after treatment, despite a similar threshold gain in the MRI+ and MRI- patients. Therefore, MRI does not seem to be predictive of the magnitude of improvement but might be considered an index of the severity of the initial cochlear damage.

In MRI+ patients, the comparison of the MRI pattern with either the pathological vHIT and the ipsi- or contralateral absence of DPOAES did not produce any significant correlation.

Despite DPOAEs (Mori et al., 2011; Zarandy et al., 2017) and vHIT (Guan et al. 2020) have been recognized as possible markers of cochlear and vestibular damage in SSHL, respectively, we were unable to find a significant correlation between MRI patterns and either diagnostic test. On one side, DPOAEs are frequently absent also in milder degrees of SNHL or even in normally hearing subjects, being rather sensitive but hardly specific. In this respect, our hypothesis is that alterations of the inner ear fluids that are detectable by current MRI methods reflect an extensive damage, much beyond the high sensitivity of DPOAEs. Conversely, alterations of the vHIT indicate the involvement of one or more semicircular canals, that in our series occurred in a minority of the patients (n=9/50, i.e. 18%).

Finally, the observed MRI patterns did not correlate with any comorbidity. This is rather surprising, as we would have expected, as an example, that the methemoglobin deposits (pattern 1) would correlate with hemorrhagic risk factors such as hypertension or the use of blood-eluting drugs; instead, we only noticed a

slight trend that could probably become significant in a much larger sample. Similarly, an "inflammatory" pattern (pattern 2) should be related with a clinical history of infection / inflammation of the middle ear or of the upper airways, which was not the case.

To our best knowledge, there have been so far no other studies in literature attempting to correlate the prognostic value of different patterns at MRI acquired in the early stage of SSHL, with the addition of Gadolinium-enhanced, 4hs-delayed acquisition.

The main limitation of this study is the small number of SSHL patients enrolled by a single institution, restraining the chance to identify any possible relationship between MRI patterns and the audiological outcomes of treatment.

A great deal of work still needs to be carried out until a complete understanding of the morphological changes at the microscopic level in the cochlear structures of SSHL patients is achieved, and until we will be able to correctly interpret these new MRI findings.

While continuing to gather more patients ourselves, we would encourage other studies to replicate our protocol, in order to share more data on the subject and increase the statistical power.

Conclusion

The experience acquired with our MRI protocol permits to affirm that early assessment by MRI in SSHL patients may provide useful information about the etiopathogenesis and, possibly, to help clinicians selecting the most appropriate treatment on an individualized basis.

In the current study, positive MRI findings generically correlated with worse audiological outcomes, but the different MRI patterns did not identify any specific prognostic model, despite rigid protocol settings. None of the aspects of the patient's clinical history or any of the audio-vestibular features were consistently associated with any of the three observed MRI patterns (hemorrhagic, inflammatory, BLB breakdown). Larger series of patients with SSHL are needed, possibly from multicentric studies, in order to sort out from advanced MRI those informations that could harvest a more significant prognostic value.

Statements

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki Declaration, as revised in 2008. The study has been approved by the Ethical Committee of Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan, Italy, identification number: 616, June 19, 2019: 473_2018).
Written informed consent was obtained from all individual participants involved in the study. Participants' anonymity has been guaranteed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Giorgio Conte, main investigator, MRI data collection, supervised data analysis.

Federica Di Berardino audiological data gathering, data collecting during the follow-up and manuscript draft.

Rodolfo Francesco Mastrapasqua, data gathering and statistical analysis, manuscript draft.

Silvia Casali neuroradiological data gathering, MRI imaging and figure editing

Elisa Scola draft manuscript, study design

Fabio Triulzi study design and reviewed the manuscript

Pasquale Capaccio clinical and laboratory data collection, revision.

Lorenzo Pignataro revision, study design and coordination

Diego Zanetti data analysis, manuscript draft and revision, study design and coordination.

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Figure Legends

Figure 1. *Pattern 1 (intra ~~labirynthine~~ labyrinthine haemorrhage).* Axial pre-contrast T1 and FLAIR images show high signal of the right vestibule compatible with the presence of intralabyrinthine metahemoglobin; axial post-contrast FLAIR image shows vestibular enhancement compatible with BLB breakdown. *Pattern 2 (acute inflammatory process).* Axial pre-contrast T1 image does not show signal abnormalities; axial pre-contrast FLAIR image shows high signal of the right cochlear middle and apical turns compatible with the presence of intralabyrinthine proteins; axial post-contrast FLAIR image shows enhancement of the right cochlear turns and vestibule compatible with BLB breakdown. *Pattern 3 (isolated BLB breakdown).* Axial pre-contrast T1 and FLAIR image do not show signal abnormalities; axial post-contrast FLAIR images show enhancement of the right cochlear turns and vestibule compatible with isolated BLB breakdown.

Figure 2. Distribution of MRI findings among the sample population

Figure 3. Pre- and post-treatment hearing thresholds (PTA 0.5-1-2-3 kHz), according to the MRI findings at admission.

Table Legends

Table I. Distribution of audiometric curves according to MRI findings

Table II. Audio-vestibular features and MRI findings in the study population

Table III. Association of comorbidities with the MRI pattern, expressed as number of cases positive for risk factor/total cases for this pattern (percentage of positives for single MRI pattern), p value is considered significant at 0.005 (Bonferroni test)

Table I. Distribution of audiometric curves according to MRI findings

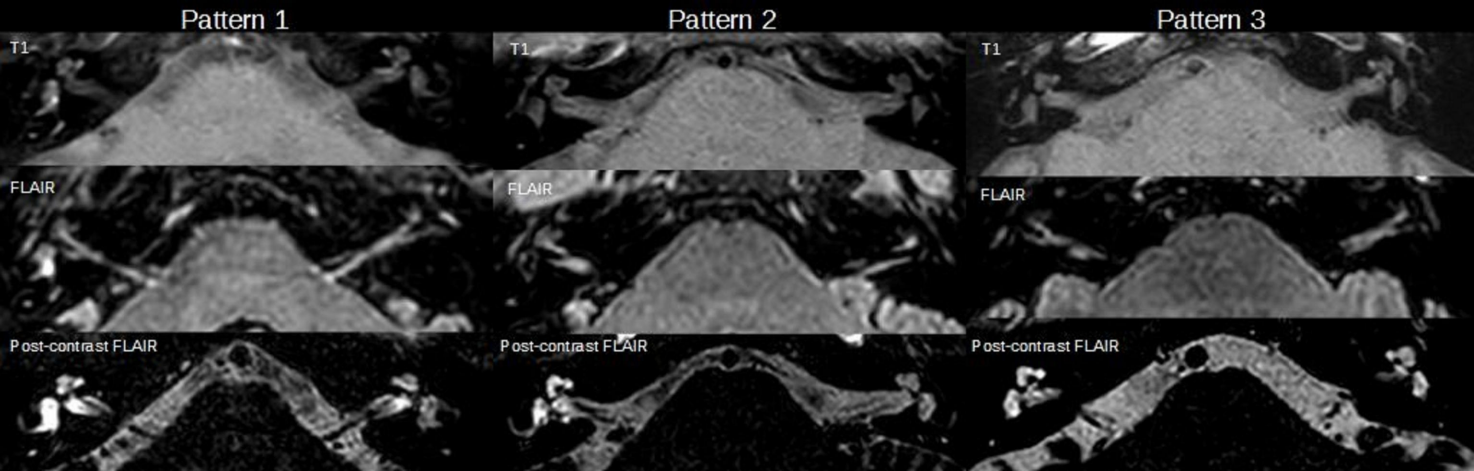
	MRI+ N=29	MRI- N=21	Bonferroni corrected significance (p=0.0125)
High-tone SSHL	16 (64.0%)	9 (36.0%)	0.284
Low-tone SSHL	0	6 (100.0%)	0.003
Flat curves	5 (55.6%)	4 (44.4%)	0.577
Profound SSHL	8 (80.0%)	2 (20.0%)	0.0110

Table II. Audio-vestibular features and MRI findings in the study population

	MRI+ **N=29**	**MRI-** **N=21**	**Significance**
Median initial PTA	67.25 ± 53.75	57.50 ± 36.25	n.s.
Median PTA 1 month	63.75 ± 40.00	21.25 ± 40.63	0.009
Median PTA improvement (at 1 month)	10.00 ± 25.63	20.00 ± 42.50	n.s.
# of patients improved at 1 month	12 (41.4%)	11 (52.4%)	0.056
# of patients with long term PTA improvement (6 months)	10 (34.5%)	15 (71.4%)	0.0023
Pathological vHIT	5 (17.2%)	4 (19.0%)	n.s
Presence of DPOAE at admission	4 (13.8%)	1 (4.8%)	n.s.
presence of DPOAE at 1 month	7 (24.1%)	5 (23.8%)	n.s.
Presence of contralateral DPOAE at admission	15 (51.7%)	10 (47.6%)	n.s.
Presence of contralateral DPOAE at 1 month	16 (53.6%)	11 (55.1%)	n.s.

Table III. Association of comorbidities with the MRI pattern, expressed as number of cases positive for risk factor/total cases for this pattern (percentage of positives for single MRI pattern), p value is considered significant at 0.005 due to Bonferroni correction

	Pattern 1	Pattern2	Pattern 3	*p* value
First episode/recurrence	4/5 (80%)	12/16 (75%)	0/8	0.30
Atherosclerosis	2/5 (40%)	6/16 (37%)	2/8 (25%)	0.78
Arterial Hypertension	2/5 (40%)	5/16 (31%)	7/8 (87%)	0.03
Coagulation disorders	0/5	1/16 (6%)	1/8 (12%)	0.68
Autoimmune diseases	0/5	3/16 (18%)	0/8	0.25
Inflammations signs	0/5	6/16 (37%)	1/8 (12%)	0.15
History of head trauma	0/5	2/16 (12%)	0/8	0.41
Obesity	0/5	1/16 (6%)	1/8 (12%)	0.68
Smoking habit	1/5 (17%)	2/16 (12%)	0/8	0.47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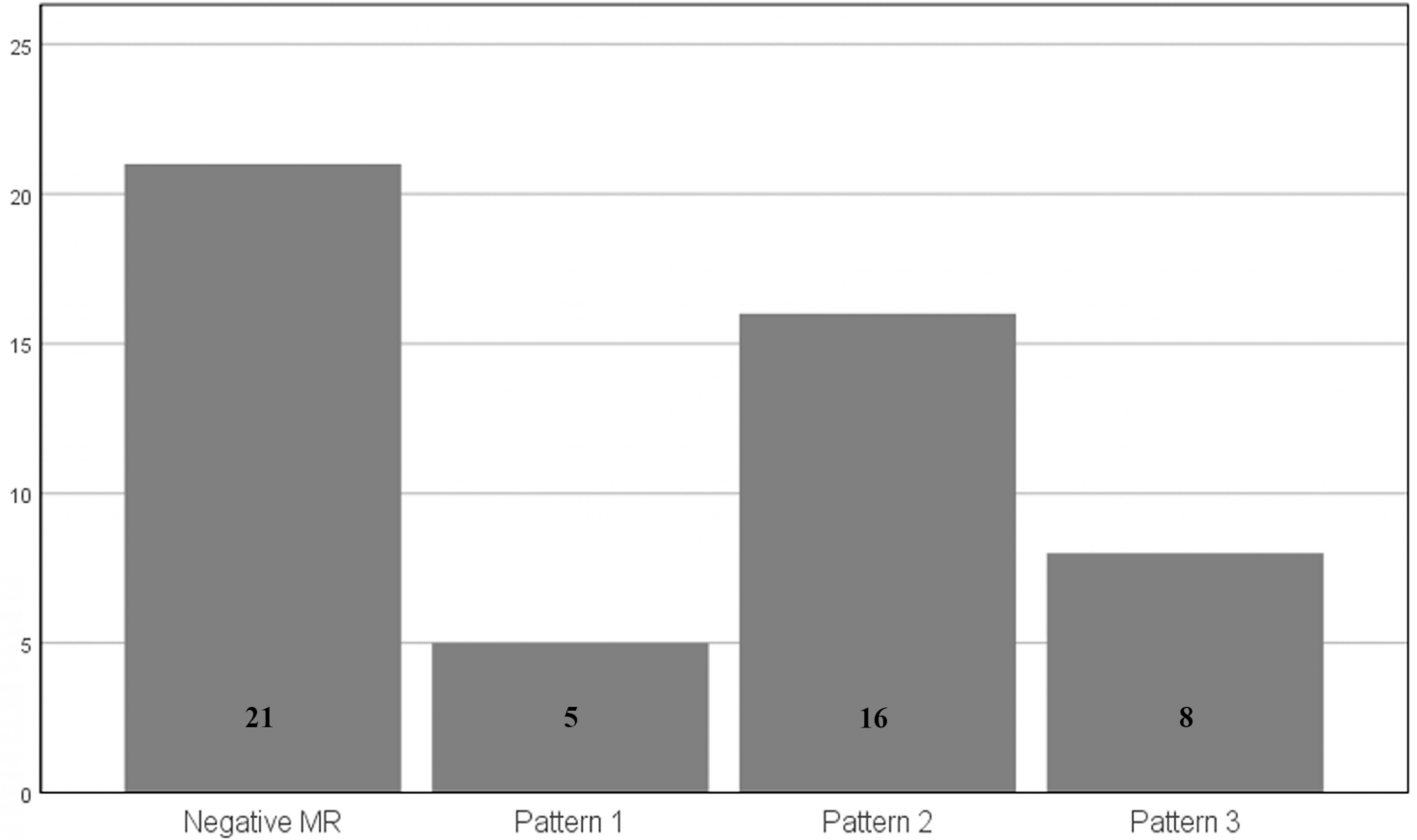
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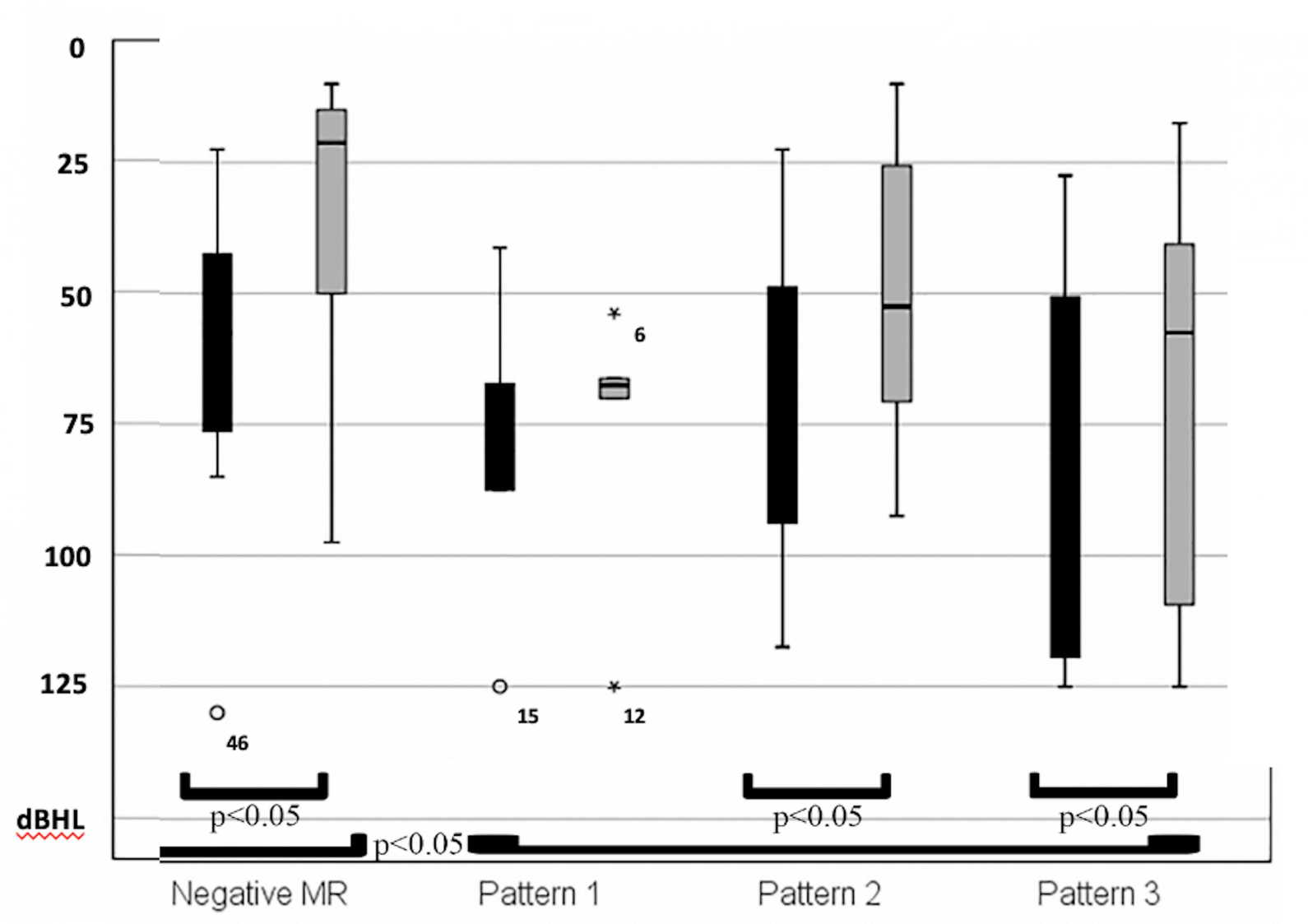
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Negative MR
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Pattern 2
Pattern 3

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