Sensorineural hearing loss (SNHL) is an unrecognized complication of common variable immunodeficiency (CVID)

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Common variable immunodeficiency (CVID) represents the most frequent form of symptomatic inborn error of immunity (IEI) [1]. Affected patients present with heterogeneous clinical manifestations, comprising increased susceptibility to infectious episodes, and a predisposition to develop autoimmune phenomena, lymphoproliferation, and neoplastic diseases [1]. In contrast to other CVID complications, sensorineural hearing loss (SNHL) has been investigated only in a small minority of CVID patients and its pathogenesis is poorly understood [2,3]. CVID patients who are diagnosed early in life and receive immunoglobulin replacement treatment (IgRT) can normally perform social and work activities and achieve a satisfying quality of life [4]. However, the onset of SNHL, if not properly recognized and treated, might lead to a significant impairment in communication and social skills, as well as an increased risk in developing dementia, depression, accidental falls, and hospitalization [5,6].

We conducted a retrospective monocentric study evaluating the occurrence of SNHL in a cohort of pediatric and adult CVID patients. CVID diagnosis was established according to the ESID Registry working definitions for clinical diagnosis of IEIs [7]. At diagnosis and during follow-up, all patients underwent audiologic testing, including pure-tone audiometry. Air and bone conduction thresholds were assessed in a sound-isolated booth, utilizing a 5 dB step and appropriate masking with narrow-band noise of the opposite ear, utilizing the plateau method. Bone threshold variability for the audiometer in subjects with normal hearing, with and without narrow-band masking, was within 10 dB, and test-retest variability was within 5 dB. SNHL was considered present when there was an impairment greater than 20 dB in at least one frequency. Fisher's exact test or Mann-Whitney test were used to compare demographical, clinical and laboratory data (at CVID diagnosis or at first immunological evaluation at our Center) from CVID patients with or without SNHL. A significance level of $p < 0.05$ was set for statistical associations. The present study included 112 CVID patients.

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All subjects are currently alive and regularly followed at the Immunology Unit of the Pediatric Clinic of ASST Spedali Civili di Brescia, University of Brescia.

Among the 112 included CVID patients, 20 of them were diagnosed with SNHL (17.86%). Acquired causes of SNHL such as professional or environmental acoustic trauma as well as exposure to ototoxic drugs were excluded. Bilateral SNHL was observed in 60% (12/20 patients) of the cohort, while 8/20 (40%) patients presented unilateral SNHL. According to the International Bureau for Audiophonology (BIAP) classification [8], hearing loss deficit was classified as mild (loss of 20-40 dB) in 7/20 patients (35%), moderate (loss of 41-70 dB) in 11/20 patients (55%), severe (loss of 71-90 dB) in 1 patient (5%), and profound (loss of 91-120 dB) in 1 patient (5%) (Figure 1A). Considering the frequencies involved, SNHL was generally detected at high frequencies (4000-8000 Hz) (17/20 patients, 85%), more rarely in a pan-tonal form (2/20 patients, 10%), and at low frequencies (250-500 Hz) (1/20 patients, 5%) (Supplememtary Figure 1). Impedance audiometry test revealed type A tympanogram in the whole cohort, hence confirming the absence of middle-ear alteration affecting the compliance or elasticity of the tympanic-ossicular system (data not shown). During the follow-up, 7/20 (35%) of the CVID patients with SNHL showed variable progression, with worsening of the hearing threshold (4/7 patients), involvement of other frequencies (3/7 patients) and evolution of the presentation mode from unilateral to bilateral (1/7 patients) (Figure 1B); none of the SNHL affected CVID patients presented spontaneous recovery of the hearing damage. These findings suggest that SNHL in patients with CVID is irreversible and can deteriorate over time. Moreover, CVID patients were diagnosed with SNHL at a median age of 40 years (interquartile range 33 – 44.5 years), which is lower than the typical age of onset of presbycusis, suggesting that SNHL could be part of the complex and heterogeneous CVID clinical manifestations. When compared to a control group of 92 CVID patients without SNHL, we observed that CVID patients with SNHL displayed a statistically significant older age (p 0.0002, Supplementary Table 1). Therefore, we can speculate that SNHL could develop also in, at least a part of, the remaining 92 CVID patients, thus warranting the importance to establish a proper audiologic follow-up for all CVID affected patients. In addition, CVID patients with SNHL were diagnosed with CVID at an older age when compared to CVID patients without SNHL (p 0.0110, Supplementary Table 1). No other statistically significant correlations were found regarding both demographical and clinical features (Supplementary Table 1). On that account, SNHL appear as an independent CVID complication rather than the result of other CVID manifestations that may lead to the development of SNHL, such as damages caused by inflammatory cytokines or bacterial/viral toxins resulting from recurrent infectious episodes. In

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addition, it has been estimated that 30% of immune-mediated SNHL is associated with other autoimmune disorder [9]; however, we did not observe any differences in terms of autoimmunity predisposition when comparing CVID patients with SNHL to CVID patients without SNHL. On laboratory point of view, CVID patients with SNHL displayed statistically significant lower levels of serum IgA and IgM when compared to CVID patients without SNHL (p 0.0045 and 0.0064, respectively), while no differences were observed in terms of lymphocyte subsets (Supplementary Figure 2). An association between SNHL and selective IgA deficiency has already been published [10] and our results confirmed a possible role of defective mucosal immunity in the development of SNHL.

In conclusion, our data reveal that SNHL is a complication that affects roughly 20% of CVID patients, highlighting the importance for audiologic screening at diagnosis and during follow-up in IEIs patients. Multicentric studies are warranted in order to confirm our findings and better define the characteristics of SNHL in CVID patients.

Abbreviations

CVID, Common variable immunodeficiency
IEI, inborn error of immunity
SNHL, sensorineural hearing loss
IgRT, immunoglobulin replacement treatment
BIAP, International Bureau for Audiophonology

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Disclosure of conflicts of interest

The authors declare no conflict of interest.

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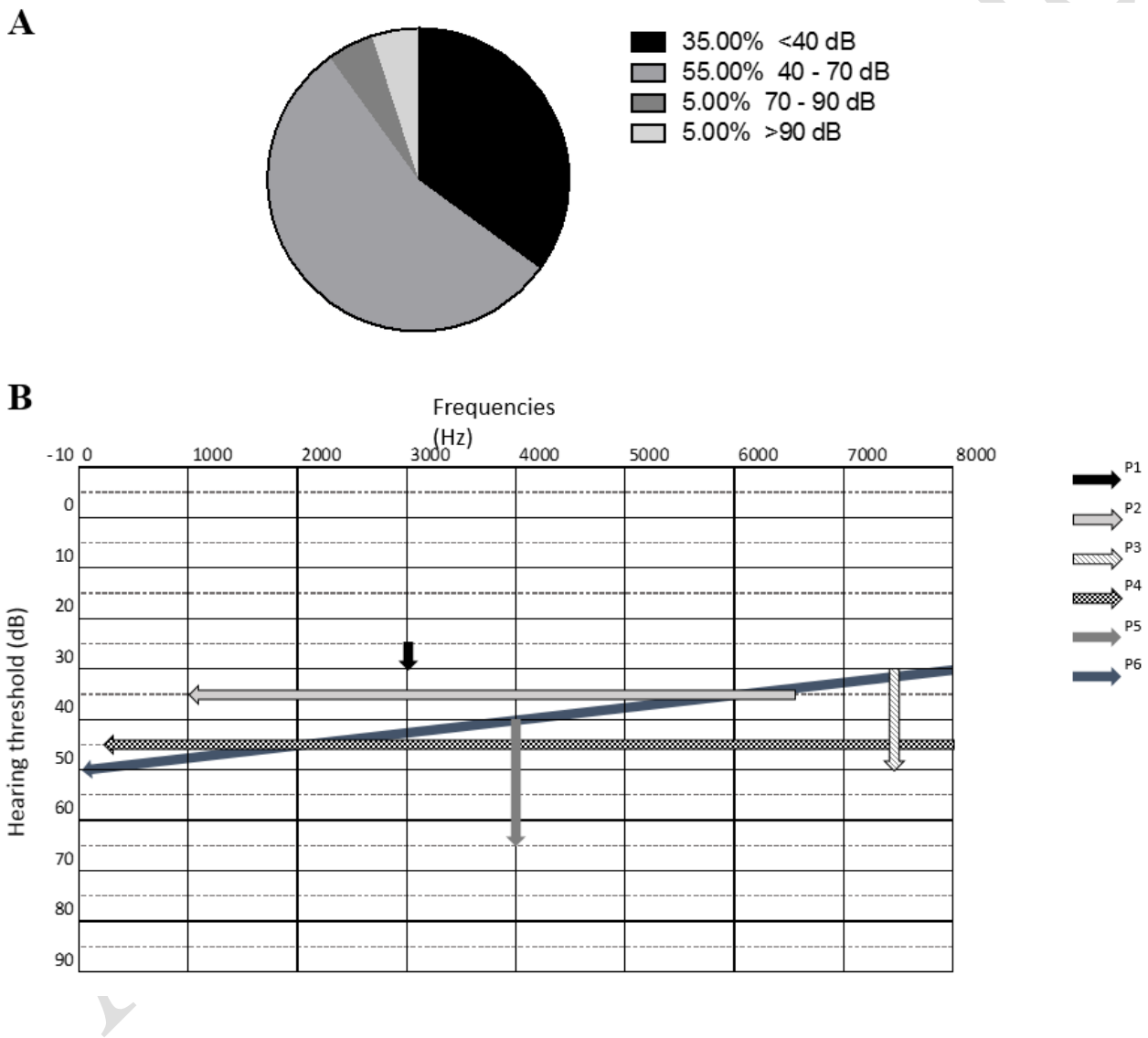
FIGURE LEGENDS

Figure 1. (A) hearing threshold loss in the 20 common variable immunodeficiency (CVID) patients with sensorineural hearing loss (SNHL). (B) progression of SNHL in 6 CVID patients as observed during the follow-up.



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