Sensorineural Hearing Loss Is an Unrecognized Complication of Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) is the most frequent symptomatic inborn error of immunity (IEI) [1]. Affected patients present with heterogeneous clinical manifestations comprising increased susceptibility to infectious episodes and a predisposition to autoimmune phenomena, lymphoproliferation, and neoplastic diseases [1]. In contrast to other complications of CVID, sensorineural hearing loss (SNHL) has been investigated 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 can perform social and work activities normally and enjoy a satisfactory quality of life [4]. However, the onset of SNHL, if not properly recognized and treated, might lead to significant impairment in communication and social skills, as well as an increased risk of dementia, depression, accidental falls, and hospitalization [5,6].

We conducted a single-center retrospective study to evaluate the occurrence of SNHL in a cohort of pediatric and adult CVID patients. CVID was diagnosed 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 soundproof booth utilizing a 5-dB step and appropriate masking with narrow-band noise of the opposite ear. The plateau method was applied. Bone threshold variability for the audiometer in patients with normal hearing, with and without narrow-band masking, was within 10 dB, and test-retest variability was within 5 dB. The patient was considered to have SNHL when impairment was greater than 20 dB in at least 1 frequency. The Fisher exact test or Mann-Whitney test was used to compare demographic, clinical, and laboratory data (at diagnosis of CVID or the first immunological evaluation

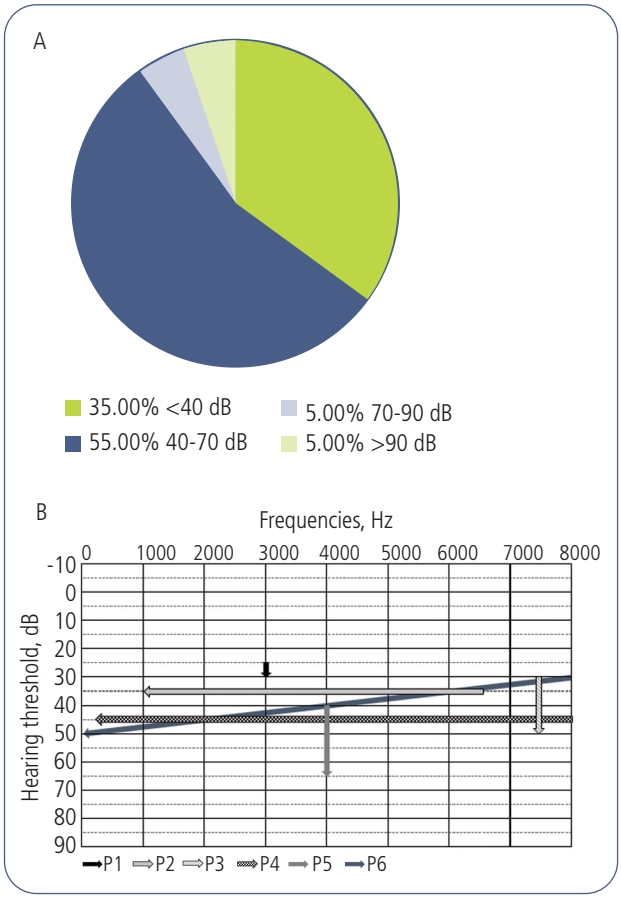

Figure. A, Hearing loss in the 20 common variable immunodeficiency (CVID) patients with sensorineural hearing loss (SNHL). B, Progression of SNHL in 6 CVID patients, as observed during follow-up.

at our center) from CVID patients with and without SNHL. Statistical significance was set at $P<.05$. The present study included 112 CVID patients. All patients are currently alive and regularly followed up at the Immunology Unit of the Pediatric Clinic of ASST Spedali Civili di Brescia, University of Brescia.

Among the 112 CVID patients included, 20 were diagnosed with SNHL (17.86%). Acquired causes of SNHL such as professional or environmental acoustic trauma and exposure to ototoxic drugs were excluded. Bilateral SNHL was observed in 12 patients (60%), while 8 patients (40%) presented unilateral SNHL. According to the International Bureau for Audiophonology classification [8], hearing loss was classified as mild (loss of 20-40 dB) in 7 patients (35%), moderate (loss of 41-70 dB) in 11 patients (55%), severe (loss of 71-90 dB) in 1 patient (5%), and profound (loss of 91-120 dB) in 1 patient (5%) (Figure, A). SNHL was generally detected at high frequencies (4000-8000 Hz) (17 patients, 85%), more rarely in a pan-tonal form (2 patients, 10%), and at low frequencies (250-500 Hz) (1 patient, 5%) (Supplementary Figure 1). Impedance audiometry testing revealed a type A tympanogram for the whole cohort, thus confirming the absence of middle-ear alteration affecting the compliance or elasticity of the tympanic-ossicular system (data not shown). During the follow-up, progression was variable for 7 of the CVID patients with SNHL (35%), with worsening of the hearing threshold (4/7 patients), involvement of other frequencies (3/7 patients), and progression of the presentation mode from unilateral to bilateral (1/7 patients) (Figure, B); none of the CVID patients with SNHL recovered spontaneously from the damage to their hearing. These findings suggest that SNHL is irreversible in patients with CVID and can deteriorate over time. Moreover, CVID patients were diagnosed with SNHL at a median (IQR) age of 40 years (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 clinical manifestations of CVID. When compared to a control group of 92 CVID patients without SNHL, we observed that CVID patients with SNHL were statistically significantly older ($P=.0002$, Supplementary Table 1). Therefore, we can speculate that SNHL could also develop in at least some of the remaining 92 CVID patients, thus warranting the need for appropriate audiologic follow-up for all patients with CVID. In addition, CVID patients with SNHL were diagnosed with CVID at an older age than CVID patients without SNHL ($P=.0110$, Supplementary Table 1). No other statistically significant correlations were found regarding either demographic or clinical features (Supplementary Table 1). SNHL was an independent complication of CVID rather than the result of other CVID manifestations that may lead to the development of SNHL, such as damage caused by inflammatory cytokines or bacterial/viral toxins resulting from recurrent infectious episodes. In addition, it has been estimated that 30% of immune-mediated SNHL is associated with other autoimmune disorders [9], although we did not observe any differences in terms of predisposition to autoimmunity when comparing CVID patients with SNHL and CVID patients without SNHL. As for laboratory data, CVID patients with SNHL had statistically significantly lower levels of serum IgA and IgM than CVID patients without SNHL ($P=.0045$ and .0064, respectively), while no differences were observed for 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 affecting roughly 20% of CVID patients, thus highlighting the importance of audiologic screening at diagnosis and during follow-up in patients with IEIs. Multicenter studies are warranted to confirm our findings and better define the characteristics of SNHL in CVID patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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