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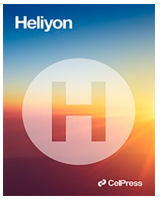

Research article

Aminoglycoside-induced sensorineural hearing loss in pediatric cystic fibrosis patients: A retrospective cohort study

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ABSTRACT

Background: Pulmonary infections by gram-negative organisms are important in cystic fibrosis (CF). Aminoglycosides (AG) are often part of the treatment regimen. However, they are a well-known cause of ototoxicity. Even minimal hearing impairment in children could have a future impact on functional well-being.
We aimed to investigate the progression of sensorineural hearing loss (SNHL) over several years in pediatric CF patients, and to identify risk factors, such as the use of AG, including both intravenous (IV) and inhaled AG.
Methods: Retrospective analyses of patient records from children and adolescents followed up at the CF clinic of the Antwerp University Hospital, Belgium, were performed. We collected data on age, sex, pure-tone audiometry, and the use of AG. Descriptive and binary logistic regression analyses, and if indicated generalized estimating equations (GEE) analyses were performed.
Results: Forty pediatric patients were enrolled in the study taking part from 2013 to 2020. Pure-tone audiometry revealed an important rate of SNHL over several years, with a prevalence of 29 % for high-frequency SNHL (i.e. 8 kHz). Increasing age was identified as a significant risk factor for the development of SNHL at 8 kHz if 5 or more IV AG courses ($p = 0.01$) were reported or when IV AG were combined with inhaled AG ($p = 0.002$).
Conclusions: Age combined with the use of IV AG ($\geq$5 courses or in combination with inhaled AG) are predictive for developing high-frequency SNHL (i.e. 8 kHz). We suggest routine annual hearing screening (incl. high-frequency thresholds) in CF patients, starting from childhood.

1. Introduction

Pulmonary infections by gram-negative organisms, especially *Pseudomonas aeruginosa* (*P. aeruginosa*), are important in cystic fibrosis (CF). Intravenous (IV) aminoglycosides (AG), such as tobramycin and amikacin, are often part of the treatment regimen. However, they are a well-known cause of ototoxicity, making CF patients prone to develop sensorineural hearing loss (SNHL) and

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vestibular hypofunction [1–8]. Amikacin is indicated having a more ototoxic potential than tobramycin [9–11]. Next to IV AG, inhaled tobramycin is increasingly used in CF patients. It allows achievement of high bronchial levels of drug with minimal systemic absorption and is known for its great activity against *P. aeruginosa*. An ototoxic effect of inhaled AG treatment has not been proven in CF patients [12]. However, one sporadic case of ototoxicity associated with inhaled tobramycin was reported in a pediatric CF patient, who presented with renal failure [13]. Moreover, one study suspected a synergistic effect between inhaled and IV AG on ototoxicity when nebulized tobramycin was used [3].

Previous studies described a prevalence of SNHL ranged from 0 % to 47 % in children with CF and the impact of cumulative lifetime IV AG on it [1,3,9,14–16]. Research on this topic has contributed to possible strategies for audiologic monitoring in these patients [1,3,4,9,10,14–20]. When receiving IV AG, it has been reported that cochlear hair cells are impacted by reactive free oxygen radicals from an iron-aminoglycoside complex, resulting in apoptotic cell death and degeneration of presynaptic ribbons in the hair cells. High-frequency outer hair cells situated at the basal end of the cochlea are affected first, followed by the inner hair cells. Spiral ganglion degeneration may occur independently or secondary to hair cell damage. A loss of high-frequency sound perception will primarily develop. With an accumulating exposure to AG, hearing loss will be finally affected at speech frequencies [1,2,10,21–23].

Despite the current novel therapies in CF, treatment of respiratory infections by gram-negative pathogens will stay relevant and only become a greater challenge with increasing survival. Clinicians will have to balance the most suitable therapeutic options against its known complications and look for alternative therapies if needed. Even minimal hearing impairment in children could have a future impact on communicative and academic skills, and consequently on functional well-being [1,14,24]. When hearing loss worsens, a combination of less cognitive load and more social isolation can trigger an accelerated cognitive decline later in life [25].

2. Purpose of the study

In this study we primarily aimed to investigate the progression of SNHL over several years in pediatric CF patients. Secondly, we aimed to identify risk factors, such as the use of AG, including both IV and inhaled AG.

3. Materials and methods

3.1. Participants

Retrospective study of patient records from children and adolescents followed up at the CF clinic of the Antwerp University Hospital, Belgium, was performed. Approval was obtained from the Ethics committee of Antwerp University Hospital (Project ID 4989 - Edge 2820). Diagnosis of CF was confirmed by a positive sweat test and/or genetics. The personal history of the patients included results from the routine hearing screening, performed on an annual basis. In case of infection with *P. aeruginosa*, patients received IV and inhaled AG following the Brompton guidelines [11]. Patients or audiometric data were excluded when risk for hearing loss was higher in one of the following circumstances: external or middle ear disease, congenital hearing loss, IV AG administered 60 or less days before audiologic testing, renal problems, too high plasma AG levels and co-administration of IV vancomycin.

3.2. Audiometric tests

Otoscopic examination and tympanometry was applied to exclude external and middle ear problems. Conventional pure-tone audiometry was performed by certified audiologists in a sound-attenuated room. An arbitrarily fixed value of 120 dB HL was assigned in cases where no measurable hearing was detected at equipment limits. Audiometry was conducted using an AC40 Clinical 2 channel audiometer (Interacoustics, Middlefart, Denmark). All audiometers were calibrated using ISO 389-I:2017 standards (https://www.iso.org/standard/69855). Air conduction hearing thresholds were collected from both ears for each subject and the following pure-tone averages (PTA) were calculated: 0.5–4 (i.e., BIAP bureau international d'audiophonologie, https://www.biap.org [0.5, 1, 2, and 4 kHz]); 4–8 (4 and 8 kHz); and 6–8 (6 and 8 kHz). The American Speech-Language-Hearing association (ASHA) criteria were used to define sensorineural hearing loss (SNHL): a hearing threshold of $>$25 dB hearing level (dB HL) at one or more frequencies and a hearing threshold of $>$15 dB HL at 2 or more adjacent frequencies.

3.3. Statistical analysis

We collected data on age, sex, pure tone thresholds, and the use of AG, including both IV and inhaled therapy. We performed a retrospective cohort study by distinguishing 2 groups: 'no SNHL over time' or 'SNHL over time'. At least two audiologic tests had to be available. If none of these tests showed SNHL, we categorized it as 'no SNHL over time'. If one test or more showed SNHL, the patient belonged to the 'SNHL over time' group. For the data analysis, we used SPSS software (version 27). An association between SNHL and a potential risk factor was examined using binary logistic regression analyses. The dependent variable was 'SNHL' and covariates were as follows: 'age at beginning of the study', 'sex', 'IV AG treatment', 'number of IV AG courses', 'number of days of IV AG', '$\geq$ 5 IV AG courses', 'IV AG in combination with inhaled AG'. If indicated, we finally used generalized estimating equations (GEE) analyses, as a method for modeling longitudinal data. To collect the repeated audiometric measurements (at least one) within one same ID subject, we transposed all data. We indicated the 'patients' ID' as the subject variable. All subjects had 6 different time points of possible audiometric measures, referred as the 'within-subject variables'. The binary response variable 'SNHL' was analyzed as a dependent variable over time. 'Age' was the only covariate. Predictors were as follows: 'Sex', 'IV AG treatment', 'number of IV AG courses',

'number of days of IV AG', '≥ 5 IV AG courses', 'IV AG in combination with inhaled AG'. Interaction between the covariate and the predictors were tested. We calculated 95 % confidence interval for an odds ratio. *P*-values of <0.05 were of statistical significance.

4. Results

Forty patients were eventually included in the study. Five patients were lost to follow up because of transfer to another CF center. Demographic and clinical data are summarized in Table 1. A baseline audiometric profile of both ears is represented in Fig. 1.

Table 2 gives an overview of the detected prevalence of SNHL over time and its significant risk factors. After performing binary logistic regression analyses, a statistically significant effect of '≥ 5 IV AG courses' ($p = 0.02$) and 'the combination of IV AG with inhaled AG' ($p = 0.04$) were only observed for high-frequency SNHL (i.e. 8 kHz). GEE analysis was than performed for the group of forty patients with at least one appropriate audiologic test at 8 kHz. We identified increasing age as the risk factor for the development of SNHL if 5 or more IV AG courses ($p = 0.01$) were reported or when IV AG were combined with inhaled AG ($p = 0.002$). Fig. 2 shows a distribution of age at the beginning of the study for the patients who developed 'SNHL over time' or 'no SNHL over time' at 8 kHz. There is likely to be a difference between the two groups. Interestingly a few children who had received no ($n = 4$; age 7–16 years) or less than 5 ($n = 1$; courses: 1; age 16 years) courses of IV AG showed SNHL as well. Moreover, of the 71 % who had normal hearing, two patients (age 20–22 years) have had 5-10 courses of IV AG and one patient (age 15 years) even 15 courses. This suggests a multifactorial AG-associated ototoxicity.

5. Discussion

After retrospectively studying the progression of SNHL in a cohort of pediatric CF patients, we identified increasing age as a significant risk factor for the development of high-frequency SNHL (i.e. 8 kHz) if 5 or more IV AG (tobramycin and/or amikacin) courses were reported or when IV AG were combined with inhaled AG (tobramycin). The prevalence of SNHL at 8 kHz was 29 %. These results correspond with previous reports, where the prevalence of SNHL is ranged from 0 % to 47 % and where CF patients with SNHL were significantly older than CF patients without SNHL [1,3,9]. Furthermore, our results can be understood by the pathophysiology of the aminoglycoside-induced high-frequency hearing loss. However, in the early stage of SNHL, before speech frequencies are affected, especially children will not actively report hearing loss and careful screening for early ototoxicity is important [1,3]. We therefore suggest routine annual hearing screening (incl. high-frequency thresholds) in CF patients, starting from childhood. As mentioned above, it seems that other factors than age could play a critical role in the final evolution to AG induced SNHL. A theory has been described about a multifactorial AG-associated ototoxicity, where the mitochondrial gene mutation 'm.1555A > G' is found to be a predisposing risk factor. Carriage of this mutation increases the risk of ototoxicity after exposure to AG even when levels are within therapeutic range [1,5,11,26]. We did not test for this mutation, which could have served as a complementary screening tool for AG induced ototoxicity. Additionally, another interesting ototoxic screening could be monitoring of the vestibular function or the onset of tinnitus. We did not screen routinely for the latter if asymptomatic, however one patient needed to stop AG because of complaints of tinnitus during an AG course, without SNHL.

Several limitations are present in this study. Firstly, the prevalence of SNHL could be underestimated because audiologic testing in the extended high-frequency region (above 8 kHz) was not included in the study. Secondly, the median time between audiograms was different across patients, thereby introducing bias by missing data. However, GEE analyses allowed us to correct as much as possible for this limitation. A prospective study could have prevented this problem. Thirdly, we did not evaluate the difference in ototoxicity between amikacin and tobramycin. However, this was not possible knowing the distribution of the AG regimes in our patients. Finally, for the identified risk factor of 'IV AG in combination with inhaled AG' on SNHL, we must be careful. 75 % of the patients who received inhaled AG, have had 5 or more IV AG courses, and 83 % of this subgroup even more than 10 courses. From the patients who didn't receive inhaled AG, 61 % received no IV AG and only 6 % received 5 or more courses of IV AG. Further research is needed for a possible synergistic effect between inhaled and IV AG on SNHL, especially in those patients who already have renal or hearing impairment and who receive other nephrotoxic or ototoxic medication.

Table 1
Demographic and clinical data.

Number of patients			n = 40
Period			2013–2020
Mean (SD) age at beginning			14 (7) years
Male:female			1:1
Included audiograms	Mean (SD) number of audiograms per patient		3 (1)
	Median time between serial test points (range)		347–516 days
IV AG	At least once		49 %
	Type	Amikacin	12 %
		Tobramycin	29 %
		Both	59 %
	≥5 courses		23 %
	+ inhaled AG (tobramycin)		20 %

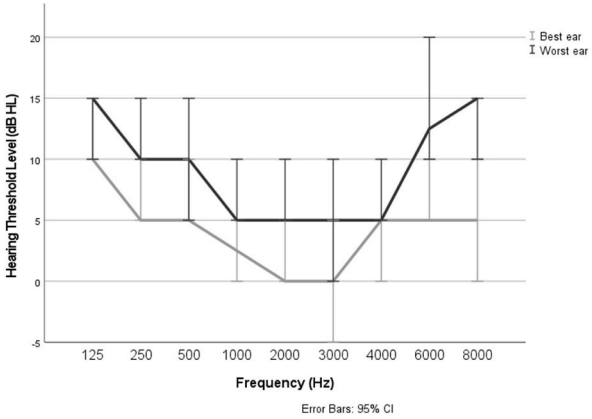

Fig. 1. Median values with 95 % confidence intervals for baseline standard (0,125 to 8 kHz) pure-tone hearing tresholds for both ears.

Table 2
Prevalence of SNHL over time and its significant risk factors.

(average) SNHL	Prevalence (%)	Significant risk factors	
		Binary logistic regression analyses	GEE analyses
>25 dB at 0,5–2 kHz	6	None	/
>25 dB at >2 freq	31	None	/
>25 dB at 1 freq	60	None	/
>15 dB at >2 adj freq	94	None	/
>25 dB at 8 kHz	29	≥5 IV AG courses (p = 0.02) IV AG + inhaled AG (p = 0.04)	Increasing age &≥5 IV AG courses (p = 0.01)IV AG + inhaled AG (p = 0.002)

/= Not applicable.

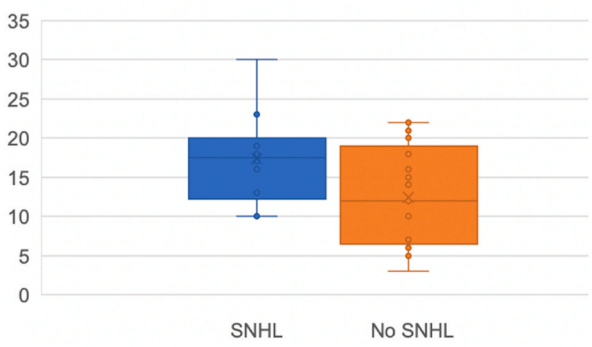

Fig. 2. Distribution of age (in years) at the beginning of the study for the patients who developed 'SNHL over time' or 'no SNHL over time' at 8 kHz.

6. Conclusion

Conventional pure tone audiometry revealed an important rate of high-frequency SNHL (i.e. 8 kHz) over several years in pediatric CF patients. Age combined with the use of IV AG (≥5 courses or in combination with inhaled AG) are predictive for developing high-frequency SNHL. These results approve the pathophysiology of AG-induced high-frequency hearing loss. We suggest routine annual hearing screening (incl. high-frequency thresholds) in CF patients, starting from childhood.

Ethics statement

The study was approved by the Ethics committee of Antwerp University Hospital (Project ID 4989 - Edge 2820) and complies with all regulations. Names of all the patients were pseudonymized.

Author contributions

Nathalie Jouret: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Nicolien Van der Poel: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. Stijn Verhulst: Writing – review & editing, Writing – original draft. Marc JW Lammers: Writing – review & editing, Writing – original draft. Vincent Van Rompaey: Writing – review & editing, Writing – original draft, Methodology, Data curation. Laure Jacquemin: Writing – review & editing. Kim Van Hoorenbeeck: Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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