Original Article

https://doi.org/10.1590/2317-6431-2021-2548

Audiology Communication Research
ISSN 2317-6431

Audiological evaluation in patients with chronic hepatitis C treated by direct-action antivirals

Avaliação audiológica em pacientes com hepatite C crônica tratados por antivirais de ação direta

Lorena Carvalho Cavalcanti Lagreca[1], *Edison Roberto Parise*[1], *João Luiz Rodrigues de Farias*[1], *Cristiana Corvaro*[1], *Marisa Frasson de Azevedo*[1]

ABSTRACT

Purpose: To verify whether treatment with hepatitis C direct-acting antivirals has adverse effects on hearing. **Methods:** The sample consisted of 16 individuals with hepatitis C virus, of both sexes, with an average age of 51 years. Individuals with conductive or mixed hearing loss who presented risk factors for hearing loss were excluded from the group. The evaluation was carried out in two moments: before the use of direct-acting antivirals and after the three-month treatment. It included the following procedures: anamnesis, external auditory canal inspection, pure tone audiometry, speech reception threshold, speech recognition index, acoustic immittance measures and transient and distortion product otoacoustic emissions. **Results:** There was a low incidence of tinnitus and vertigo. There was no statistically significant difference between the results of the pre- and post-treatment assessment. **Conclusion:** The treatment with direct-acting antivirals against the hepatitis C virus did not cause any adverse effects on hearing function.

Keywords: Hearing; Hearing Loss; Hepatitis C; Cochlea; Direct-acting antivirals

RESUMO

Objetivo: Verificar se o tratamento com os antivirais de ação direta para a hepatite C provocam efeitos adversos na audição. **Métodos:** A casuística foi composta por 16 indivíduos portadores do vírus da hepatite C, de ambos os gêneros, com média de idade de 51 anos. Foram excluídos do grupo indivíduos com perda auditiva do tipo condutiva ou mista e que apresentassem fatores de risco para perda auditiva. A avaliação foi realizada em dois momentos: antes do uso dos antivirais de ação direta e após o término do tratamento de três meses. Incluiu os seguintes procedimentos: anamnese, inspeção do meato acústico externo, audiometria tonal liminar, limiar de recepção de fala, índice de reconhecimento de fala, medidas de imitância acústica e emissões otoacústicas evocadas por estímulo transiente e produto de distorção. **Resultados:** Houve baixa ocorrência de zumbido e vertigem. Não houve diferença estatisticamente significativa entre os resultados da avaliação pré-tratamento e pós-tratamento. **Conclusão:** O tratamento com antivirais de ação direta contra o vírus da hepatite C não provocou efeitos adversos na função auditiva.

Palavras-chave: Audição; Perda auditiva; Hepatite C; Cóclea; Antivirais de ação direta

Study carried out at Setor de Audiologia da disciplina dos Distúrbios de Audição do Departamento de Fonoaudiologia da Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brasil.

[1]Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brasil.

Conflict of interests: No.

Authors' contribution: LCCL participated in the research of journals related to the theme, writing the article, collection, analysis and interpretation of research data; ERP and JLRF participated in the selection of patients indicated for research and in the article review; CC participated in the audiological examinations; MFA participated in the study design, guidance and supervision of the theoretical foundation, as well as the audiological examinations performed.

Funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), processo nº 130499/2017-0.

Corresponding author: Lorena Carvalho Cavalcanti Lagreca. lorena_cavalcanti@hotmail.com

Received: November 04, 2021; **Accepted:** April 01, 2022

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease worldwide. Estimates show that 71 million people are infected with HCV worldwide, many of whom are unaware of the infection, and that about 400,000 will die each year due to complications of this disease, mainly due to cirrhosis and hepatocellular carcinoma (HCC)[1,2].

For many decades, the standard treatment for chronic HCV infection has been the combination therapy of pegylated interferon (Peg-IFN) and ribavirin (RBV) for 24 or 48 weeks. However, this combination is associated with significant adverse effects[3]. Ototoxicity is cited as one of these side effects[4]. In fact, unilateral or bilateral sensorineural hearing loss (SSHL) has been reported as a consequence of these treatments[5-7] and sudden hearing loss may occur in about 1% of these patients[8].

However, the introduction of new direct-acting antivirals (DAA) for the treatment of hepatitis C has been changing the epidemiological landscape of this disease worldwide. The high cure rates, the excellent tolerability profile and the shorter duration of treatment enabled effective strategies to combat the disease[9].

Brazil is among the countries that stand out in this scenario. In 2015, the Ministry of Health incorporated the first direct action antivirals for the treatment of hepatitis C, within the scope of the Unified Health System (SUS). At the time, SUS provided the following drugs for the treatment of chronic hepatitis C: daclatasvir; simeprevir; sofosbuvir; the combination of the drugs ombitasvir, dasabuvir, veruprevir and ritonavir-3D; the combination of ledipasvir and sofosbuvir and the combination of elbasvir and grazoprevir, which may or may not be associated with alfapeginterferone (PEG-IFN-α) and RBV[9]. A Brazilian study reported virological cure rates around 95% among patients treated with these medications[10].

In the literature, few studies have investigated hearing in HCV patients treated with these new medications and there is no reference to whether such medications would have ototoxicity potential[11]. However, the authors recommend further studies in this area to evaluate the safety of these drugs concerning the auditory system[3,12,13]. Moreover, research on otoacoustic emissions has been recommended for hearing monitoring since they identify cochlear dysfunctions before the hearing loss[6].

Thus, this scenario motivated the study on the hearing of patients with hepatitis C virus using different combinations of the antivirals mentioned above, in addition to the research of otoacoustic emissions. Therefore, this study aimed to verify if the treatment with direct action antivirals for hepatitis C causes adverse effects on hearing.

METHODS

This is a prospective longitudinal study (pre and post-treatment of three months), conducted in the Speech-Language Pathology and Audiology sector of the Federal University of São Paulo - UNIFESP. The study was approved by the Research Ethics Committee of the institution under opinion number 3,203,427, and all participants signed the informed consent form.

The sample was recruited for convenience. The sample consisted of 16 patients, with a mean age of 51 years. Of these, eight were medicated with the compound 3D- ombitasvir, dasabuvir, veruprevir and ritonavir; five with sofosbuvir and simeprevir; two with sofosbuvir and ledipasvir and one with sofosbuvir and daclatasvir. Only one patient had viral load of HCV detected after treatment.

Patients who presented conductive and mixed hearing loss, exposure to noise, presence of otosclerosis, use of chemotherapy or radiotherapy, or use of other ototoxic drugs, family history of hearing loss and otological surgeries were excluded from the sample.

To characterize the hearing of patients, audiological evaluations were pre-scheduled in two moments: before the use of direct action antivirals proposed by the Brazilian Ministry of Health and after the end of treatment.

The audiological evaluation consisted of anamnesis, inspection of the external auditory canal, pure tone audiometry, speech audiometry, acoustic immittance measurements, and evoked otoacoustic emissions.

In the anamnesis, a questionnaire was applied in a closed set, to collect information about the patient's history and meet the exclusion criteria. An analysis of the patients' medical records was also performed to obtain information on genotypes (type 1, 2, 3 or 4), among other data.

The inspection of the external auditory canal was performed with the TK otoscope to rule out the presence of foreign bodies or the existence of excess cerumen, which could compromise the performance of the proposed tests. The individuals were subjected to pure tone audiometry in an acoustic booth, with the AD-229 audiometer, Interacoustics brand, TDH-39 earphones properly calibrated according to ANSI 3.6 standard (*American National Standards Institute*)[14]. The air conduction auditory thresholds (AV) were investigated in the frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 6000 Hz and 8000 Hz, with the descending technique[15]. Thresholds above 25 dB, at frequencies of 0.5 to 4 kHz, justified the need for bone conduction (BV) research. Hearing thresholds were considered normal when equal to or less than 25 dBHL. Thresholds above 25 dBHL were considered as hearing loss. The degree of hearing loss was classified according to the average frequencies of 500 Hz, 1000 Hz and 2000 Hz[16].

In speech audiometry, the speech reception threshold (SRT) was researched, with a list of trisyllable words, with a loud voice and with a decrease in intensity, until finding the minimum level of intensity at which each individual was able to correctly recognize 50% of the verbal stimuli presented. The speech recognition index (SRPI) was obtained by presenting a list of 25 monosyllabic words, separately, to each ear. The test was performed at a fixed intensity of 40 dBNS (above the tonal mean 500 Hz, 1000 Hz and 2000 Hz). A success rate higher than 88% of the stimuli presented was considered normal[17].

Acoustic immittance measurements were obtained with the InteracousticS middle ear analyzer, model AT 235, with a 226 Hz probe, calibrated according to ANSI 3.6/ ISO 389 (*International Organization for Standardization*). This is an objective examination to evaluate tympanic-ossicular integrity, detecting tympanometric curves classified as A, B, C, Ad and Ar[18]. Moreover, the acoustic reflex was investigated at frequencies of 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz, considering as normal the presence of the reflex from 70 dB to 90 dB above the audiometric threshold[18].

For the research of otoacoustic emissions, a cochlear analyzer of otoacoustic emissions ILOv6, of the brand Otodynamics

Ltda, was used in an acoustically treated booth, connected to a microcomputer.

For transient evoked otoacoustic emissions (TOAE), nonlinear clicks with regular pulses of 80 milliseconds duration, of rarefied polarity, presented in a series of 260 cycles per second, in a 20 ms, were used. As for the emission spectrum, the standard stimulus contains energy distributed between 500 Hz and 5 kHz. TEOAE was considered to be present when there were emissions 3 dB above noise in the frequency bands from 1 to 4 kHz, with reproducibility of the response and probe stability greater than 70%[19].

Distortion product otoacoustic emissions (DPOAE) were evoked by two pure tones, presented simultaneously, with very close sound frequencies (f1/f2=1.22). The response component considered was 2f1-f2 with intensity level of the f1 stimulus of 65 dBNPS and f2 of 55 dBNPS. In the analysis of responses, the amplitude and the signal/noise ratio were considered in the frequencies of 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz. A response was considered present when the response amplitude was positive, with a signal/noise ratio above 6 dB and noise amplitude below zero (negative)[20].

Considering all the evaluations performed, the final diagnosis was defined as: normal hearing sensitivity = hearing thresholds lower than or equal to 25 dBHL in audiometry with the presence of transient evoked otoacoustic emissions and distortion product; cochlear hearing loss = hearing thresholds higher than 25 dBHL and absence of otoacoustic emissions; cochlear dysfunction = hearing thresholds lower than or equal to 25 dBHL with absent or partial otoacoustic emissions.

For statistical analysis, the significance level considered was 10%, due to the sample size. The Chi-square test of independence (Bussab and Morettin, 2017) was applied to associate audiometry and TEOAE and DPOAE. To compare the pre- and post-treatment moments, the McNemar Pagano and Gauvreau (2004) test was applied[20].

RESULTS

The sample consisted of 16 individuals, 4 males and 12 females, from 18 to 76 years old and mean age of 51 years.

Regarding the characterization of the sample as to genotype, auditory symptoms and metabolic alterations, 15 patients (93.8%) presented genotype 1 and only one patient (6.3%) presented genotype 2. Regarding symptoms, only one patient (6.3%) complained of tinnitus and two patients (12.5%) complained of vertigo. Regarding metabolic changes, 2 participants had diabetes (12.5%) and one (6.3%) had insulin resistance. No patient had liver cirrhosis and 5 (31.2%) had previously undergone treatment with Peg-IFN and/or ribavirin. Figure 1 shows the characterization of the sample regarding genotype, auditory symptoms and metabolic alterations.

Regarding the association between the results of audiometry before and after treatment, there was no difference between the results. There were 75% normal hearing thresholds before and after treatment (Table 1).

Regarding the association between the results of transient evoked otoacoustic emissions (TEOAE), before and after treatment, the McNemar test[20] showed no evidence of difference between the results. There was 62.5% presence of TEOAE, without modification after treatment. Two cases (12.5%) showed improvement with the appearance of TEOAE after treatment (Table 2).

Regarding the association between the results of distortion produced otoacoustic emissions (DPOAE), before and after treatment, the McNemar test[20] showed no evidence of change in the results: 62.7% of the patients presented absence of DPOAE. Three cases (18.7%) showed improvement, with the appearance of post-treatment DPOAE (Table 3).

Regarding the final audiological diagnosis of the 16 patients, considering the results of pure tone audiometry, TEOAE and DPOAE (normal, cochlear hearing loss or cochlear dysfunction), the McNemar test[20] showed no significant difference. There was 25% cochlear hearing loss and 37.5%% cochlear dysfunction before and after treatment. There was improvement in three patients who presented cochlear dysfunction before treatment and started to have emissions, presenting normal audiological diagnosis after treatment (Table 4).

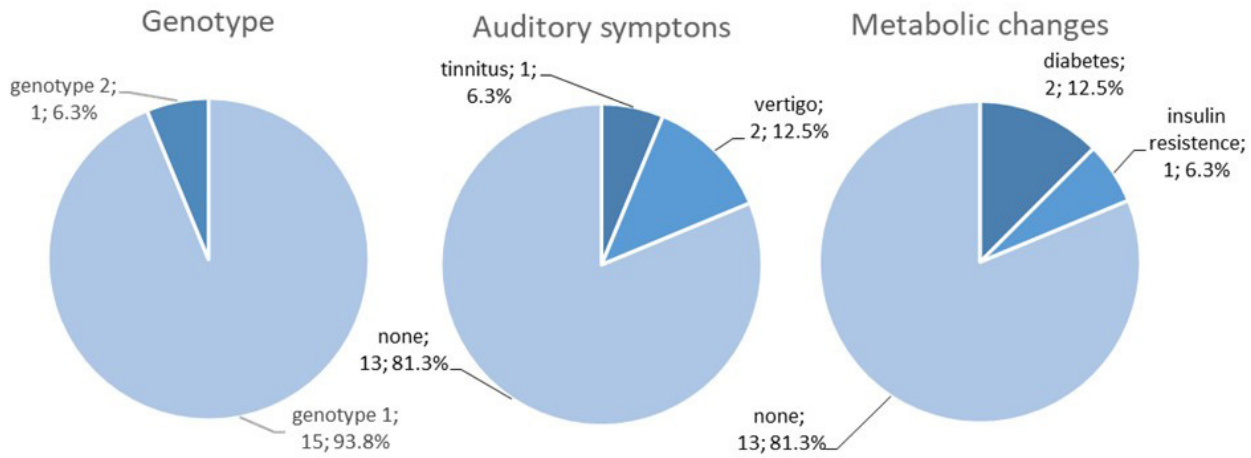

Figure 1. Distribution of the population regarding genotype variables, auditory symptoms and metabolic changes
Subtitle: % = percentage

Table 1. Audiometry results comparing pre- and post-treatment (n = 16)

		Post-treatment		Total
		normal	hearing loss	
pretreatment	normal	12 (75%)	0 (0.0%)	**12 (75%)**
	hearing loss	0 (0.0%)	4 (25%)	**4 (25%)**
Total		**12 (75%)**	**4 (25%)**	**16 (100%)**

Subtitle: n = number of patients; % = percentage

Table 2. Results of transient otoacoustic emissions comparing pre and post-treatment (n = 16)

		Post-treatment		Total
		present	absent	
pretreatment	present	10 (62.5%)	1 (6.25%)	**11 (68.8%)**
	absent	2 (12.5%)	3 (18.7%)	**5 (31.2%)**
Total		**12 (75%)**	**4 (25%)**	**16 (100%)**
p-value >0.999				

Subtitle: n = number of patients; % = percentage

Table 3. Results of distortion-produced otoacoustic emissions comparing pre and post-treatment (n = 16)

		Post-treatment		Total
		present	absent	
pretreatment	present	3 (18.75%)	0 (0.0%)	**3 (18.75%)**
	absent	3 (18.75%)	10 (75.0%)	**13 (81.25%)**
Total		**6 (37.5%)**	**10 (62.5%)**	**16 (100%)**
P-value =0.250				

Subtitle: n = number of patients; % = percentage

Table 4. Results of the final audiological diagnosis pre- and post-treatment (n = 16)

		Post-treatment			Total
		Normal	Cochlear dysfunction	Hearing loss	
Pretreatment	Normal	3 (18.75%)	0 (0.0%)	0 (0.0%)	**3 (18.75%)**
	Cochlear dysfunction	3 (18.75%)	6 (37.5%)	0 (0.0%)	**9 (56.25%)**
	Hearing loss	0 (0.0%)	0 (0.0%)	4 (25%)	**4 (25%)**
	Total	**6 (37.5)**	**6 (37.5%)**	**4 (25%)**	**16 (100.0%)**
P-value =0.250					

Subtitle: n = number of patients; % = percentage

DISCUSSION

Most patients had genotype 1 (Figure 1). This data confirms the literature, which reports genotype 1 as the most prevalent worldwide, including Brazil[2,10]. The genome of hepatitis C virus has a high degree of genetic variability. Different types of genotypes have a different response to antiviral treatment, as well as a different geographical distribution. Genotypes 1, 2 and 3 are widely disseminated around the world. Genotype 1 represents the most aggressive class of HCV, evidencing a longer treatment time when compared with genotypes 2 and 3[9]. Regarding auditory symptoms, there was a low occurrence of tinnitus and vertigo complaints. In the literature, tinnitus and vertigo have been reported in patients with hepatitis during or after treatment with previously used medications, PegINF and/or ribavirin. A study with 13 patients who received Peg-IFN and ribavirin showed that three developed tinnitus after the end of treatment[5]. In another study, with 74 patients, there was an increase in tinnitus in 31.1% of them at the end of treatment with PegINF and/or ribavirin[7]. Another study, which also confirms these data, followed 73 patients who received Peg-IFN and observed tinnitus in 32 (43.8%) patients during therapy[21]. Considering that hearing loss can occur in 0.1 to 1% of patients treated with Peg-IFN, tinnitus complaint could appear as an associated symptom[22]. The occurrence of tinnitus described in the literature, with the use of the drug previously recommended, was high (from 23.1% to 43.8%). In this study, the occurrence of tinnitus was 6.3%, a symptom present before treatment and without modification after medication, which demonstrates the absence of a relationship between direct-acting antivirals and auditory symptoms. In fact, as the new medication was not associated with the occurrence of hearing loss (Table 1), tinnitus was not expected and may have occurred from other causes.

Vertigo is rarely reported in the literature in patients with hepatitis C virus. In a study with 24 hepatitis B and C virus carriers and 30 subjects in the control group, there was no statistical difference of the complaint of vertigo between the groups[6]. Other authors also did not find the complaint of vertigo in patients with hepatitis virus[6-8]. In this study, the complaints of vertigo did not increase during and after treatment, which

showed the absence of a relationship between direct-acting antivirals and auditory symptoms.

Most of the sample (75%) presented TEOAE (Table 2), revealing normal cochlear function. There was no worsening after treatment, which indicates that the currently recommended medication did not reduce cochlear function. In two cases, there was improvement after treatment, with the appearance of TEOAE. In three cases (18.7%), there was improvement with the appearance of DPOAE after treatment.

This improvement could be related to the reduction of metabolic changes with the cure of the disease. On the other hand, there was no distortion produced otoacoustic emissions in the pretreatment with normal hearing thresholds (Table 3), indicating a cochlear dysfunction. Cochlear dysfunction is characterized by the presence of normal audiometry and alteration of otoacoustic emissions[23-26]. Currently, it is discussed that the diagnostic investigation by means of conventional tests represents a microscopic view of the auditory function[26,27]. Thus, the use of otoacoustic emissions (TEOAE and DPOAE) began to contribute to the understanding of cochlear function since they allow the evaluation of the integrity of the outer hair cells of the cochlea and identify cochlear dysfunctions before the alteration in audiometry[6]. This test has been an important tool in the early detection of cochlear alterations, since there may be diffuse lesion in more than 30% of the outer hair cells before any hearing loss is detected in the audiogram[23,24]. This is the reason why otoacoustic emissions are recommended for hearing monitoring in individuals exposed to occupational noise, using chemotherapy and ototoxic drugs[5]. Thus, they would also be indicated for auditory monitoring of patients with hepatitis C.

To justify the cochlear dysfunction present in patients with hepatitis C, the literature reports the pathophysiological mechanisms of the association between hepatitis virus infections and the development of sensorineural hearing loss remain uncertain[28,29]. Some authors suggest that hearing loss could occur due to acute exacerbation or chronic viral reaction in the mechanism of aggression to the cochlea[28,30]. Viruses can access the inner ear by hematogenous route and induce an autoimmune reaction or severe pathophysiological changes, resulting in reduced blood flow to the inner ear, often reversible, but which can be extremely destructive and result in permanent hearing loss[29,30].

The recovery of post-treatment TEOAE and DPOAE could indicate that cochlear dysfunction occurred due to changes in metabolism caused by hepatitis C and, therefore, would improve after disease remission.

Unfortunately, the literature is limited as to the occurrence of cochlear dysfunctions in patients with hepatitis C, probably due to the fact that the use of otoacoustic emissions to detect cochlear dysfunctions is still recent. Most studies used otoacoustic emission tests only to compare differences before and after treatment. Although the studies report that otoacoustic emissions identify auditory alterations before the audiogram, they did not mention the possible cochlear dysfunctions in the pretreatment[3,5-7].

Previous studies comparing pre- and post-treatment hearing with pegylated interferon and ribavirin have found a decrease in otoacoustic emissions, characterizing cochlear dysfunctions and permanent hearing loss as a result of treatment[5-7] This combination of antivirals is associated with significant adverse effects[3], and unilateral or bilateral sensorineural hearing loss (SSHL) is reported as one of its consequences[6,7]. This study showed no change in the results of the audiological evaluation performed before and after treatment with the new direct action antivirals. Both audiometric thresholds and otoacoustic emissions showed no significant changes with the use of medications, suggesting that these antivirals, currently recommended, cause no hearing loss.

This finding agrees with the results of a recent study in 80 patients with chronic hepatitis C virus, who received combination therapy of new direct-acting antivirals (sofosbuvir and ribavirin), and who were evaluated pre-treatment and post-treatment, suggesting that this therapy does not cause noticeable effects on cochlear functions[3].

Likewise, the results of this study agree with those obtained in an overview of drug-induced ototoxicity, based on the analysis of reports from the database of the Italian national pharmacovigilance network, contemplating adverse reactions, such as hearing loss and tinnitus, from 2001 to 2017. This study revealed only three cases of tinnitus related to sofosbuvir/ledipasvir and the authors considered that hypoacusis and tinnitus in the use of these antivirals would not be expected. They also reported that no information on ototoxicity associated with direct action antivirals against hepatitis C is available in the literature[12].

The findings of this study are similar to those obtained in the literature, which do not consider the use of antivirals sofosbuvir and simeprevir as a risk factor for hearing loss[13]. Nevertheless, the authors suggest a careful observation for several months after the administration of interferons and antivirals for the treatment of HCV infections[13].

As a limitation factor of this study, the sample was considered small, due to the difficulty of obtaining the medicines provided by SUS in a given period of data collection and the evasion of some patients who did not return after treatment. Due to the small sample, one suggests to further this theme with new studies, including pure tone audiometry and research of otoacoustic emissions in the auditory monitoring of patients treated for hepatitis C.

Although the literature is still limited on the effect of direct action antivirals on hearing function, requiring further studies in this area[12,13], this study showed that the currently recommended medication produce no side effects on hearing.

CONCLUSION

Treatment with direct-acting antivirals against hepatitis C virus cause no adverse effects on hearing function.

ACKNOWLEDGEMENTS

To the volunteer patients, an essential part of the development of this research. To the entire faculty of the hepatitis sector of UNIFESP and the Graduate Program of the Speech Therapy/Human Communication Disorders course of UNIFESP/EPM, for the opportunity and support in the elaboration of this research. To Prof. Dr. Ellen Osborn, for the encouragement and great help with the provision of material for the accomplishment of this research. To Prof. Dr. Denise Botter, for the statistical analysis

of the data of this study. To CNPq, for the financial assistance that made it possible to carry out this work.

REFERENCES

1. European Union HCV Collaborators. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(5):325-36. http://dx.doi.org/10.1016/S2468-1253(17)30045-6.
2. WHO: World Health Organization. Hepatitis C [Internet]. 2019 [citado em 2019 Jul 10]. Disponível em: http://www.who.int/mediacentre/factsheets/fs164/en/
3. Ismail EI, Morgan AE, Farag RE. Assessment of auditory functions in chronic hepatitis C patients treated by sofosbuvir. J Otol. 2018;13(1):10-5. http://dx.doi.org/10.1016/j.joto.2017.11.001. PMid:29937860.
4. Lee CA, Mistry D, Uppal S, Coatesworth AP. Otologic side effects of drugs. J Laryngol Otol. 2005;119(4):267-71. http://dx.doi.org/10.1258/0022215054020485. PMid:15949078.
5. Casale M, Mazzarelli C, Vespasiani Gentilucci U, Potena M, Pappacena M, Faiella F, et al. Distortion-product otoacoustic emissions: a useful test for monitoring ototoxicity induced by pegylated interferon and ribavir in treatment in patients with chronic hepatitis C. Int J Immunopathol Pharmacol. 2012;25(2):551-6. http://dx.doi.org/10.1177/039463201202500229. PMid:22697091.
6. Sharifian MR, Kamandi S, Sima HR, Zaringhalam MA, Bakhshaee M. Clinical study INF-α and ototoxicity. BioMed Res Int. 2013;2013:1-4. http://dx.doi.org/10.1155/2013/295327.
7. Asal S, Sobhy O, Ismail O, Bedewy E. Study of the effect of combined interferon and ribavirin therapy on the hearing profile of hepatitis C virus patients. Egyptian J Otolaryngol. 2015;31:237-43.
8. Piekarska A, Jozefowicz-Korczynska M, Wojcik K, Berkan E. Sudden hearing loss in chronic hepatitis C patient suffering from Turner syndrome, treated with pegylated interferon and ribavirin. Int J Audiol. 2007;46(7):345-50. http://dx.doi.org/10.1080/14992020701261413. PMid:17680465.
9. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde e Departamento de DST A e HV PCDT. Protocolo clínico e diretrizes terapêuticas para hepatite viral C e coinfecções [Internet]. Brasília: Ministério da Saúde; 2018 [citado em 2019 Abr 25]. Disponível em: http://conitec.gov.br/images/Relatorios/2018/Relatorio_PCDT_HepatiteC.pdf
10. Lobato CMO, Codes L, Silva GF, Souza AFM, Coelho HSM, Pedroso MLA, et al. Direct antiviral therapy for treatment of hepatitis C: A real-world study from Brazil. Ann Hepatol. 2019;18(6):849-54. http://dx.doi.org/10.1016/j.aohep.2019.08.001. PMid:31537509.
11. Cianfrone G, Pentangelo D, Cianfrone F, Mazzei F, Turchetta R, Orlando MP, et al. Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. Eur Rev Med Pharmacol Sci. [Internet]. 2011 [citado em 2022 Mar 10];15:601-36. Disponível em: http://www.europeanreview.org/wp/wp-content/uploads/956.pdf
12. Barbieri MA, Cicala G, Cutroneo PM, Mocciaro E, Sottosanti L, Freni F, et al. Ototoxic adverse drug reactions: a disproportionality analysis using the italian spontaneous reporting database. Front Pharmacol. 2019;10:1161. https://doi.org/10.3389/fphar.2019.01161.
13. Tanaka M, Hasegawa S, Nakao S, Shimada K, Mukai R, Matsumoto K, et al. Analysis of drug-induced hearing loss by using a spontaneous reporting system database. Plos One. 2019;14(10):e0217951. https://doi.org/10.1371/journal.pone.0217951.
14. ANSI: American National Standard Institute. American national standard specification for audiometers (ANSI 3.6). New York: ANSI; 1969.
15. Katz J. Tratado de audiologia clínica. 4ª ed. São Paulo: Manole; 1999.
16. Silman S, Silverman CA. Basic audiologic testing. In: Silman S, Silverman CA. Auditory diagnosis: principles and applications [Internet]. San Diego: Singular Publishing Group; 1997 [citado em 2018 Out 5]. Disponível em: http://www.scielo.br/scielo.php?script=sci_nlinks&ref=000138&pid=S1809-48642012000300005000021&lng=pt
17. Jerger J, Silverman CA. Binaural interference: a guide for audiologistis. San Diego: Plural Publishing INC.; 2018. Chapter 3, The wiring diagram of the auditory system; p. 29.
18. Jerger J. Clinical experience with impedance audiometry. Arch Otolaryngol. 1970;92(4):311-24. http://dx.doi.org/10.1001/archotol.1970.04310040005002. PMID: 5455571.
19. Finitzo T, Albright K, Neal JO. The newborn with hearing loss: detection in the nursery. Pediatrics. 1998;102(6):1452-60. http://dx.doi.org/10.1542/peds.102.6.1452. PMid:9832584.
20. Gorga MP, Stover L, Neely ST, Montoya D. The use of cumulative distribuitions to determine critical values and levels of confiance for clinical distortion product otoacoustice mission measurements. J Acoustic Soc Am. 1996;100(2 Pt 1):968-77. http://dx.doi.org/10.1121/1.416208.
21. Kanda Y, Shigeno K, Matsuo H, Yano M, Yamada N, Kumagami H. Interferon-induced sudden hearing loss. Audiology. 1995;34(2):98-102. http://dx.doi.org/10.3109/00206099509071903. PMID: 8561688.
22. Dusheiko G. Side effects of α interferon in chronic hepatitis C. Hepatology. 1997;26(3, Suppl 1):112S-21S. http://dx.doi.org/10.1002/hep.510260720. PMid:9305675.
23. Bohne B, Clark WW. Growth of hearing loss and cochlear lesion with increasing duration of noise exposures. In: Homenik AP, Henderson D, Salvi R. New perspectives on noise-induced hearing loss. New York: Raven Press. p. 283-302.
24. Fiorini AC, Fischer FH. Emissões otoacústicas por transiente evocado em trabalhadores expostos a ruído ocupacional. Revista Distúrbios da Comunicação. 2000;11(2):167-91.
25. Azevedo M. Emissões otoacústicas. In: Figueiredo M. Emissões otoacústicas e BERA. São José dos Campos (SP): Pulso; 2003. p. 35-83.
26. Corrêa GF, Russo ICP. Autopercepção do handcap em deficientes auditivos adultos e idosos. Rev CEFAC. 1999;1(1):54-63.
27. Plomp R. The intelligent ear. London: Lawrence Erlbaum; 2002. p. 1-11.
28. Nasab MS, Fathololoomi MR, Alizamir A. Association between hepatitis B and hearing status. Oman Med J. 2012;27(5):418-20. http://dx.doi.org/10.5001/omj.2012.103. PMid:23074556.
29. Schuknecht HF, Donovan ED. The pathology of idiopathic sudden sensorineural hearing loss. Arch Otorhinolaryngol. 1986;243(1):1-15. PMid:3707419.
30. Huang CC, Lin WB, Chang PH, Chan KC, Lee TJ. Sudden deafness as a presenting symptom of chronic hepatitis B with acute exacerbation. Otolaryngol Head Neck Surg. 2009;141(5):659-60. http://dx.doi.org/10.1016/j.otohns.2009.05.006. PMid:19861211.