Evaluation of Hearing in Patients with Multiresistant Tuberculosis

Avaliação da Perda Auditiva em Doentes com Tuberculose Multirresistente

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ABSTRACT

Introduction: Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis constitute a major threat to worldwide tuberculosis control. The treatment demands the use of a therapeutic regimen in second-line drugs for a minimum period of 20 months, which includes aminoglycosides over a period of about eight months. These are associated with permanent cochleovestibular changes.

Material and Methods: This cross-sectional study aims to evaluate the auditory function in individuals who completed treatment for multidrug-resistant tuberculosis (with scheme that included aminoglycosides) at the Center of Regional Reference for multidrug-resistant tuberculosis located in the North of Portugal, between the years 2009 and 2012. Patients who met the inclusion criteria were submitted to tonal and vocal audiograms, otoacoustic emissions at 2000-5000 Hz frequencies, and a tympanogram.

Results: Between 2009 and 2012, 27 patients were referred to the Centre of Regional Reference for multidrug-resistant tuberculosis, in the North Region of Portugal, resulting in five deaths. Of the 22 individuals invited, 11 attended. These were aged between 31 and 59 years (41 ± 10). Amikacin was used in 80% of patients. Six patients (60%) had sensorineural hearing loss.

Discussion/ Conclusion: The results of this study suggest the need for a more frequent audiological monitoring in patients with multidrug-resistant tuberculosis treated with aminoglycosides allowing early detect hearing loss.

Keywords: Aminoglycosides; Hearing Loss/ chemically induced; Tuberculosis, Multidrug-Resistant.

RESUMO

Introdução: A tuberculose multirresistente e a extensivamente resistente constituem atualmente a principal ameaça ao controlo da tuberculose a nível mundial. O seu tratamento exige o uso de um esquema terapêutico com fármacos de segunda linha por um período mínimo de 20 meses, onde se incluem aminoglicosídeos durante um período de cerca de oito meses. Estes estão associados a alterações cocleovestibulares permanentes.

Material e Métodos: Estudo transversal que pretende avaliar a função auditiva em indivíduos que terminaram tratamento por tuberculose multirresistente (com esquema que incluia aminoglicosídeos) no Centro de Referência Regional para a Tuberculose Multirresistente da Sub-Região de Saúde do Norte entre os anos de 2009 e 2012. Os doentes que preencheram os critérios de inclusão foram convocados para a realização de: exame objetivo otorrinolaringológico, audiograma tonal e vocal, otoemissões acústicas por produtos de distorção nas frequências de 2000-5000 Hz e timpanograma.

Resultados: Entre 2009 e 2012 foram referenciados 27 casos para o Centro de Referência para a tuberculose multirresistente da Região Norte, tendo-se verificado cinco óbitos. Dos 22 indivíduos convocados, compareceram 11. Estes possuíam idades compreendidas entre os 31 e os 59 anos (41 ± 10). A amicacina foi usada em 80% e a capreomicina nos restantes. Seis (60%) dos utentes estudados apresentaram surdez neurossensorial. As otoemissões acústicas foram negativas em todos os doentes com hipoacúsia neurossensorial, o que confirma a sua origem coclear.

Discussão/ Conclusão: Os resultados deste estudo sugerem a necessidade de existir uma monitorização audiológica mais frequente nos indivíduos com tuberculose multirresistente tratados com aminoglicosídeos permitindo detectar mais precocemente a perda auditiva.

Palavras-chave: Aminoglicosídeos; Perda Auditiva; Tuberculose Multirresistente.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) defined as the simultaneous presence of resistance to isoniazid and rifampin, and extensively-drug resistant tuberculosis (XDR-TB), considered as MDR-TB with associated resistance to any fluoroquinolone plus at least to one of the following – amikacin, kanamycin or capreomycin – in strains of *Mycobacterium Tuberculosis*[1-4] and in coinfection with HIV, is currently the major threat to the worldwide control of tuberculosis.[5,6] Treatment requires the use of an alternative therapy regimen including second-line drugs for a 20-month minimum period of time[3], including aminoglycosides for approximately 8 months. These are associated to permanent cochlear and vestibular damage.[1-10]

The National Reference Centre for MDR-TB (*Centro de Referência Nacional para a TB-MDR*) was founded and published in June 2007 by the Portuguese Health General Directorate (*Direção Geral da Saúde* [*DGS*] - nº 14/DT (5th June 2007). This document proposed the creation of Regional Reference Centres for MDR-TB in each of the five continental Health Regions and in Madeira.

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The North Health Region Reference Centre for MDR-TB (*Centro de Referência Regional para a TB-MDR da Região de Saúde do Norte* [*CRRTB-MDR-Norte*] was launched within the Fight Against Tuberculosis Program of the North Regional Health Administration 2008-2010 (*Programa de Luta Contra a Tuberculose da Administração Regional de Saúde do Norte 2008-2010*), responsible for the follow-up and support to treatment of patients with MDR-TB in this region.

Referral of patients undergoing MDR-TB treatment to the ENT Department is routinely performed at the *CRRTB-MDR-Norte* reference centre.

MATERIAL AND METHODS

This cross-sectional descriptive study aimed to assess the auditory function in patients having completed their treatment for MDR-TB/XDR-TB (with an aminoglycoside regimen) at the *CRRTB-MDR-Norte* over the 2009-2012 timeframe. Patients with congenital hearing loss or cochlear disorders prior to treatment, as well as those with known conductive hearing loss or with abnormal findings in otoscopic examination at the time of treatment completion were excluded from the study.

The patients meeting inclusion criteria were called to attend to ENT examination and underwent the following: (1) pure-tone audiometry and speech audiometry, (2) high frequency pure-tone audiometry (8-16 KHz), (3) distortion-product otoacoustic emissions testing (DPOAE) in the 2,000-5,000 Hz frequency range and (5) tympanometry. The presence of any cochlear symptoms, current or previous to TB-treatment, patient's occupational and noise exposure history, type of tuberculosis (pulmonary, extrapulmonary or disseminated), ototoxic medications, as well as treatment duration were assessed in the ENT examination.

Air and bone conduction were tested and pure-tone average (PTA) was calculated (average of auditory thresholds at the 500-4,000 Hz frequency range). A 25 dB hearing loss (HL) threshold was defined, above which hearing loss was considered.. This was ranked in:

I – mild hearing loss: 26-40 dB HL PTA;

II – moderate hearing loss: 41-70 dB HL PTA;

III – severe hearing loss: 71-90 dB HL PTA;

IV – profound hearing loss: ≥ 91 dB HL PTA.

Speech Reception Threshold (SRT) was calculated in the pure-tone audiometry testing. DPOAE were ranked as present or absent and tympanometry results as type A, B or C.

RESULTS

In total, 27 patients with MDR-TB or XDR-TB were referred to the *CRRTB-MDR-Norte* over the 2009-2012 timeframe and 5 deaths (18.5%) occurred in patients with co-morbidities (Table 1).

Table 1A - Evaluation of hearing function in patients with MDR-TB attending to the CRRTB-MDR-Norte (continued)

Patient Number			HEARING FUNCTION				
	Age (years)	Side	Type of TB	Ototoxic medication	Treatment duration (months)	End of treatment (months)	Tympanometry (type)
1	31	Right Left	P[1]	Amikacin	4	31	A A
2	44	Right Left	P[1]	Amikacin	6	36	A A
3	59	Right Left	P[1]	Amikacin	6	22	A A
4	36	Right Left	P[1]	Amikacin	5	24	A A
5	41	Right Left	D[2]	Capreomicina	8	4	A A
6	31	Right Left	P[1]	Amikacin	8	23	A A
7	53	Right Left	P[1]	Amikacin	7	19	A A
8	32	Right Left	P[1]	Amikacin	6	11	A A
9	49	Right Left	P[1]	Capreomycin	8	30	A A
10	34	Right Left	E[3]	Amikacin	8	1	A A

[1] Pulmonary; [2] Disseminated; [3] Extrapulmonary.

Our study involved 11 (7 female) of the 22 patients that were called for examination, corresponding to a 50% response rate. One patient with congenital hearing loss was excluded from the study. MDR-TB was found in all the patients. None of the patients presented with any cochlear or vestibular symptom or any abnormal finding in otoscopic examination prior to treatment.

The average age of the ten patients included in the study was 41 (± 10) and 4 to 8 months (6.6 ± 1.4) was the time duration of treatment with ototoxic medications. The early interruption of treatment was commonly associated to the development of renal or auditory toxicity.

Amikacin was the most frequently used medication (80%).

A 65% incidence rate of hearing loss was found in our study, corresponding to 13/20 ears: 2/20 (10%) with mild, 7/20 (35%) with moderate and 2/20 (10%) with severe and profound neurosensory hearing loss, respectively.

The auditory average thresholds on each tested frequency (125-16,000 Hz) are shown in Fig. 1.

DISCUSSION

To our knowledge, this is the first study carried out in Portugal regarding the assessment of hearing loss in patients with MDR-TB or XDR-TB treated with ototoxic drugs.

Hearing loss is one the most devastating side effects of aminoglycoside in resistant tuberculosis. It is believed to be related to external ciliated cell apoptosis triggered by reactive oxygen species generation,[2,9] which may explain for the absence of DPOAE in patients with hearing loss found in our study. The damage to the external ciliated cells starts at the base of the cochlea and progress to the apex and to the Organ of Corti in more severe forms, with hearing loss initially occurring at high frequencies.[2,3,4,6] The average auditory thresholds across frequencies are shown in Fig 1. The lack of consensus regarding the definition of hearing loss and the high variability in the evaluation methodologies are reflected in the 21.3% to 70.1% variability found in literature.[2,3,5,7,10] Nevertheless, it should be pointed out that the percentage of patients with hearing loss is higher in prospective studies, in which there is a standardized evaluation and involving all the patients, suggesting that the clinically less significant forms of hearing loss may go unnoticed in smaller studies and with less robust methodologies.

Few factors are known that may clearly increase susceptibility to the ototoxicity caused by aminoglycoside. Most risk factors described in animal models are difficult to prove or do not correlate in human studies. Even though animal studies have demonstrated that ototoxicity is more prevalent with higher dose, frequency of administration and treatment duration,[11] a systematic review of 48 studies

Table 1B - Evaluation of hearing function in patients with MDR-TB attending to the CRRTB-MDR-Norte (conclusion)

Patient Number	HEARING FUNCTION							
	Tympanometry (type)	DPOAE	PTA/SRT (dB)	High-frequency (KHz) audiogram (dB)				Otoscopy
				8	10	12.5	16	
1	A	Absent	26/30	65	60	80	∞	Normal
	A	Absent	33/20	60	55	70	∞	
2	A	Absent	100/∞	∞	∞	∞	∞	Normal
	A	Absent	100/∞	∞	∞	∞	∞	
3	A	Absent	65/55	75	70	∞	∞	Normal
	A	Absent	60/90	90	80	∞	∞	
4	A	Absent	62/55	105	95	∞	∞	Normal
	A	Absent	54/57	85	70	∞	∞	
5	A	Present	14/37	15	15	40	∞	Normal
	A	Present	12/27	30	30	55	∞	
6	A	Present	23/37	80	90	∞	∞	Normal
	A	Present	24/23	70	75	∞	∞	
7	A	Absent	53/50	95	∞	∞	∞	Normal
	A	Absent	58/50	85	∞	∞	∞	
8	A	Absent	84/∞	105	∞	∞	∞	Normal
	A	Absent	80/∞	100	∞	∞	∞	
9	A	Present	17/27	35	70	70	∞	Normal
	A	Absent	35/33	95	80	∞	∞	
10	A	Present	10/20	5	5	5	30	Normal
	A	Present	9/15	10	5	5	30	

[1] Pulmonary; [2] Disseminated; [3] Extrapulmonary.

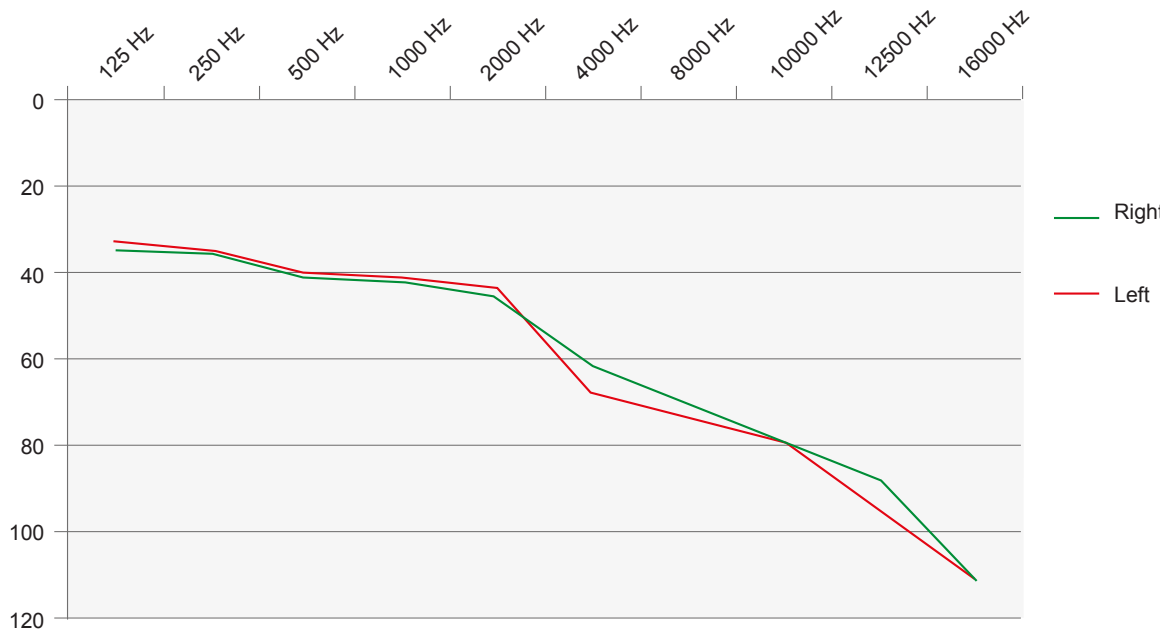

Figure 1 - Patient hearing-loss average thresholds (measured on a dB HL [hearing loss] scale) across several frequencies

published in 2010 has failed to support these claims.[12] The same happened with other factors as patient's age, gender or tobacco consumption.[2,3,5,7] Genetic predisposition is a well-known risk factor. The A1555G mutation in mitochondrial DNA is associated to non-syndromic hearing loss and increases susceptibility to ototoxicity caused by aminoglycoside.[13] In the future, screening of this mutation with genetic testing may be useful in order to recognize patients more susceptible to ototoxic cochlear damage.

As this form of hearing damage is permanent and irreversible, monitoring of hearing function is crucial during treatment with ototoxic medications. Although there is a shared understanding among the different medical associations[4], it is accepted that hearing function should be tested before starting treatment with an audiogram and at least monthly thereafter up to 3-6 months upon discontinuation.[4,6,9,14] This assessment should include the frequencies above 8,000 Hz in order to increase the test's sensitivity since hearing loss starts and is more severe in higher frequencies, as already described. Any 20 dB loss on a single frequency or 10 dB in two contiguous frequencies should warn the physician about of ototoxicity.[14] Whenever this is detected, treatment interruption, doses and frequency reduction or change to a less ototoxic medication are available options. This decision should be individualized and should depend on clinical severity, duration of treatment, sensitivity profile of the strain, availability of efficient and safe alternatives, as well as on hearing loss severity and progression.

The fact that this was a retrospective study, without any baseline or pre-treatment hearing evaluation confers a major limitation to the study. In addition we cannot exclude a selection bias due to the participation of patients with hearing loss symptoms. Despite the exclusion of any patients with hearing loss symptoms previous to the administration of the ototoxic medications, this does not ensure that the patients involved in the study had no other subclinical forms of hearing loss with a possible major impact on our evaluation. This fact increases the need for prospective studies with a larger sample of patients to be carried out, perhaps nationwide, involving the five MDR-TB Regional Reference Centres (*Centros de Referência Regionais para a TB-MDR*).

CONCLUSION

The high incidence of hearing loss found in our study increases the need to establish operation protocols in close relationship among the Reference Centres and the ENT Departments, in order to improve early detection and referral of hearing loss.

OBSERVATIONS

This manuscript was presented as a poster to the 61st *Congresso da Sociedade Portuguesa de Otorrinolaringologia e Cirurgia Cérvico-Facial*, Lisbon, 1-4th May 2014.

CONFLICTS OF INTEREST

The authors declare there were no conflicts of interest in writing this manuscript.

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