Audiological Evaluation and Analysis of Patients with Malignancy Treated with Cisplatin Chemotherapy

Sudeep Madisetti[1]

[1]Associate Professor, Department of ENT, RVM Medical Sciences and Research, Siddipet, Telangana, India.

ABSTRACT

BACKGROUND

Ototoxicity is defined as the pharmacological adverse reaction affecting the inner ear or auditory nerve, characterized by cochlear or vestibular dysfunction. Cisplatin used most frequently in the treatment of malignancies is an ototoxic agent. Evidence has shown that early detection of toxicity through prospective ototoxicity monitoring allows for consideration of treatment modifications to minimize or prevent permanent hearing loss and balance impairment. We wanted to conduct audiological evaluation of patients on chemotherapy with Cisplatin to evaluate the development of hearing loss and report.

METHODS

A retrospective study was conducted over a period of 3 years. All patients were subjected to thorough ENT examination, audiological evaluation including air and bone thresholds, pure tone average, speech discrimination and DPOAE. In addition, complete haemogram, liver and renal function tests were performed to evaluate the fitness for chemotherapy. Serial audiograms are taken at the end of each cycle up to 06 cycles of chemotherapy. Follow-up audiograms are taken at 03 months and 06 months after completion of chemotherapy.

RESULTS

Audiological evaluation among the 72 patients before the commencement of chemotherapy showed that 52 patients had normal hearing with air thresholds ranging from 10 to 20 dB with a mean of 14.45 ± 1.05 dB, bone thresholds ranging from 05 to 10 dB with a mean of 09.45 ± 0.35 dB. The pure tone average was ranging from 15 to 20 dB with a mean of 17.15 ± 1.75 dB. The speech discrimination score was 80 to 85%. The DPOAE values were present and normal in all the patients (100%). Among the 52 patients with normal hearing 07/52 (13.46%) had developed moderate hearing loss and among the 20 patients with pre-existing hearing loss, 04 / 20 (20%) patients had developed severe sensorineural hearing loss in this study.

CONCLUSIONS

Among the 52 patients with normal hearing 07 / 52 (13.46%) had developed moderate hearing loss and among the 20 patients with pre-existing hearing loss, 04 / 20 (20%) patients had developed severe sensorineural hearing loss in this study. Hence audiologic monitoring is important in patients undergoing Cisplatin chemotherapy and post-chemotherapy auditory monitoring is essential to rehabilitate the patients with sensorineural hearing loss.

KEYWORDS

Ototoxicity, Hearing Loss, Pure Tone Audiometry, Distortion Product of Otoacoustic (DPOAE) Emission, PTA and Audiological Evaluation

Corresponding Author:
Dr. Sudeep Madisetti,
Associate Professor,
Department of ENT,
RVM Medical Sciences and Research, Siddipet, Telangana, India.
E-mail: sudeepent@gmail.com

DOI: 10.18410/jebmh/2020/314

How to Cite This Article:
Madisetti S. Audiological evaluation and analysis of patients with malignancy treated with cisplatin chemotherapy. J. Evid. Based Med. Healthc. 2020; 7(30), 1490-1494. DOI: 10.18410/jebmh/2020/314

Submission 05-05-2020,
Peer Review 02-06-2020,
Acceptance 17-06-2020,
Published 27-07-2020.

BACKGROUND

Certain pharmacological agents including antibiotics, anti-malignancy chemotherapeutic agents and diuretics cause side effects like cellular degeneration of cochlear and / or vestibular tissues leading to its functional deterioration called as Ototoxicity.[1] These therapeutic agents or ototoxic drugs can act on the cochlea, vestibular system or both. There are nearly more than 600 categories of drugs which have the potential to cause ototoxicity.[2] Aminoglycosides, platinum-based chemotherapeutic agents, loop diuretics, macrolide antibiotics, and antimalarials are the commonly used ototoxic drugs[3] against various infections and malignancies in children and adults. Among the platinum-based chemotherapeutic agents Cisplatin is used in the treatment of Neuroblastoma, osteosarcomas, hepatoblastoma, germ cell tumours, medulloblastoma, and other paediatric cancers.[4] But Cisplatin commonly causes sensorineural hearing loss that is bilateral, irreversible, and may progress over time.[5] It affects all ages. However in children especially during speech acquiring age it causes debilitating hearing loss leading to impaired language acquisition in nearly 60% of children causing difficulty with learning and psychological development, and subsequent reduction in social functioning that will affect them for the remainder of their lives.[6, 7] Ototoxicity due to Cisplatin occurs in adults between 23% and 50% in adults.[8] In some studies rise in hearing thresholds were observed in nearly 100% of patients who were administered Cisplatin.[9,10] The ototoxicity due to Cisplatin is dose dependent and cumulative in nature; can be influenced by factors such as age, gender, and co-morbid conditions like congestive heart failure, renal failure, hypertension, genetic susceptibility, geographic factors, type of drug, and route of administration, duration of therapy, bio-availability and pre-existing hearing loss.[11] With this background a study was conducted to conduct audiological evaluation of patients on chemotherapy with Cisplatin to know the development of hearing loss and report.

METHODS

A Retrospective study was conducted in the Department of ENT in RVM Institute of Medical Sciences and Research, Siddipet, Telangana. Medical case records of 79 patients were obtained from the medical records section for over a period of 3 years from Dec 2016 to Nov 2019 to collect the data. An Institutional ethical committee clearance was obtained before the commencement of the study.

Inclusion Criteria

- Patients aged 18 years to 78 years of both genders were included.
- Patients with malignancy irrespective of their histological type fit and eligible to undergo chemotherapy with Cisplatin were included.

Exclusion Criteria

- Patients with less than 18 years of age, with prior history of ear disease, ear surgery, noise exposure, trauma, suffering with chronic diseases such as diabetes/ hypertension and undergoing chemotherapy with other platinum group of drugs were excluded from study.
- Patients with previous history of severe to profound sensorineural hearing loss were excluded.

All the patients were subjected to thorough ENT examination, audiological evaluation including Air and Bone thresholds, pure tone average, speech discrimination and DPOAE. In addition, complete haemogram, liver and renal functions were performed to know the fitness for chemotherapy. Serial audiograms are taken at the end of each cycle up to 06 cycles of chemotherapy. Follow-up audiograms are taken at 03 months and 06 months after completion of Chemotherapy. Among 79 patients, 04 patients were defaulters for further treatment and 03 patients died during the course of treatment. Among the remaining 72 patients, head and neck carcinoma patients were treated with the dose of 40-60 mg/sqm. Patients with lung, stomach and Neuro-ectodermal carcinoma patients were treated with 60 mg/sqm. Patients with ovarian, nasopharyngeal carcinoma and patients with malignant Brenner tumour were treated with 75 mg/sqm. Patients with breast and pancreatic carcinoma patients were treated with a maximum of 50 mg/sqm. Patients with oesophageal and cervical carcinoma patients were treated with 40–60 mg/sqm. All patients were treated for 3 days with three divided doses.

RESULTS

Among 72 patients who completed chemotherapy with Cisplatin 47 were males and 25 were females with a male to female ratio of 1.88: 1. Patients in this study belonged to the age group of 18 to 75 years with a mean age of 46.30 ± 4.90 years. Among them 15 patients had Head and Neck carcinomas, 13 had Bronchogenic carcinoma, 12 had stomach carcinoma, 09 patients had carcinoma cervix, 06 patients had carcinoma breast, 05 patients had peri ampullary carcinoma of pancreas, 4 patients had ovarian carcinoma, 04 had oesophageal carcinoma, 02 patients had had non-Hodgkin's lymphoma, 01 patient had Neuro-ectodermal tumour and 01 patient had malignant Brenner tumour (Table 1).

Among the 15 patients with head and neck carcinoma, 07/15 (46.66%) patients had carcinoma of oral cavity, 03/15 (20%) had carcinoma oropharynx, 02/15 (13.33%) patients had carcinoma Hypopharynx, 02/15 (13.33%) patients had Carcinoma larynx and 01/15 (06.66%) patient had carcinoma of nasopharynx (Table 2).

Among the 72 patients, 39 (54.16%) patients had stage III, 21 (29.16%) patients were in stage IV, 07 (09.72%) patients had stage II and 05 (06.94%) patients were in stage I malignancy (Table 3).

Type of Carcinoma	Male	Female	M:F Ratio
Head and Neck carcinomas- 15	10	05	2:1
Bronchogenic carcinoma- 13	11	02	5.5:1
Stomach carcinoma- 12	10	02	5:1
Carcinoma cervix- 09	00	09	-
Carcinoma breast- 06	00	06	-
Peri ampullary carcinoma of pancreas- 05	03	02	1.5:1
Ovarian carcinoma- 04	0	04	-
Oesophageal carcinoma- 04	03	01	3:1
Non-Hodgkin's lymphoma- 02	01	01	1:1
Neuro-ectodermal tumour- 01	01	-	-
Malignant Brenner tumour- 01	00	01	-

Table 1. Incidence and Gender Distribution of Various Carcinomas in the Study (n-72)

Types of Head Neck Carcinomas	No.	%
Carcinoma Oral cavity- 07	07	46.66%
Carcinoma Oropharynx- 03	03	20%
Carcinoma Hypopharynx- 02	02	13.33%
Carcinoma of Larynx- 02 Carcinoma of	02	13.33%
Carcinoma of Nasopharynx- 01	01	06.66%

Table 2. Types of Head and Neck Carcinomas in the Study (n-15)

Stage of Carcinoma	Number	Percentage
Stage I	05	06.94
Stage II	07	09.72
Stage III	39	54.16
Stage IV	21	29.16

Table 3. Incidence of Different Stages of Malignancy Cases in the Study (n-72)

In this study the incidence of histological grading of malignant tumours was analysed and found that there were 13/72 (18.05%) Patients with Histological grade I tumours, and 27/72 (37.50%) patients with grade II tumours and 32/72 (44.44%) patients with grade III tumours (Table 4).

Histological Grading	Number	Percentage
Grade I	13	18.05
Grade II	27	37.50
Grade III	32	44.44

Table 4. Histological Grading of the Malignant Tumours in the Study (n-72)

Audiological evaluation among the 72 patients before the commencement of chemotherapy showed 52/72 patients had normal hearing with Air thresholds ranging from 10 to 20 dB with a mean of 14.45 ± 1.05 dB, Bone thresholds ranging from 05 to 10 dB with a mean of 09.45 ± 0.35 dB. The pure tone average was ranging from 15 to 20 dB with a mean of 17.15 ± 1.75 dB. The speech discrimination score was 80 to 85%. The DPOAE values were present and normal in all the patients (100%), (Table 5).

Audiological Tests	Range Values	Mean Values
Air conduction	10 to 20 dB	14.45 ± 1.05 dB
Bone conduction	05 to 10 dB	09.45 ± 0.35 dB
PTA	15 to 20 dB	17.15 ± 1.75 dB
Speech discrimination score	80 to 85%	83.45 ± 1.90%
DPOAE	Present and Normal	Present and Normal

Table 5. Audiological Evaluation Prior to Chemotherapy in Patients with Normal Hearing (n-52)

In the remaining 20/72 patients with pre-existing hearing loss the audiological evaluation showed Air thresholds ranging from 30 to 40 dB with a mean of 31.85 ± 4.25 dB, Bone thresholds ranging from 15 to 30 dB with a mean of 19.45 ± 4.05 dB. The pure tone average was ranging from 25 to 40 dB with a mean of 27.25 ± 6.85 dB. The speech discrimination score was 75 to 85%. The DPOAE values were present and normal in all the patients (100%), (Table 6).

Audiological Tests	Range Values	Mean Values
Air conduction	30 to 40 dB	31.85 ± 4.25 dB
Bone conduction	15 to 30 dB	19.45 ± 4.05 dB
PTA	25 to 40 dB	27.25 ± 6.85 dB
Speech discrimination score	75 to 85%	78.65 ± 2.10%
DPOAE	Present and Normal	Present and Normal

Table 6. Audiological Evaluation Prior to Chemotherapy in Patients with Previous Loss of Hearing (n-20)

Audiological evaluation of the 52/72 patients with normal hearing after chemotherapy showed Air thresholds ranging from 45 to 60 dB with a mean of 48.75 ± 5.15 dB, Bone thresholds ranging from 25 to 40 dB with a mean of 29.75 ± 3.05 dB. The pure tone average was ranging from 35 to 48 dB with a mean of 37.85 ± 4.65 dB. The speech discrimination score was 69 to 75%. The DPOAE values were present but not normal in all the patients (Table 7).

Audiological Tests	Range Values	Mean Values
Air conduction	45 to 60 dB	48.75 ± 5.15 dB
Bone conduction	25 to 40 dB	29.75 ± 3.05 dB
PTA	35 to 48 dB	37.85 ± 4.65 dB
Speech discrimination score	69 to 75%	69.35 ± 3.40%
DPOAE	Present and not Normal	Present and not Normal

Table 7. Audiological Evaluation after Chemotherapy in Patients with Normal Hearing (n-52)

In the remaining 20/72 patients with pre-existing hearing loss the audiological evaluation showed ranging from 45 to 70 dB with a mean of 51.85 ± 5.45 dB, Bone thresholds ranging from 35 to 40 dB with a mean of 37.05 ± 42.95 dB. The pure tone average was ranging from 45 to 55 dB with a mean of 52.55 ± 5.45 dB. The speech discrimination score was 60 to 70%. The DPOAE values were absent in all the patients (100%), (Table 8).

Audiological Tests	Range Values	Mean Values
Air conduction	45 to 70 dB	51.85 ± 5.45 dB
Bone conduction	35 to 40 dB	37.05 ± 2.95 dB
PTA	45 to 55 dB	52.55 ± 5.45 dB
Speech discrimination score	60 to 70%	78.65 ± 2.10%
DPOAE	Absent	Absent

Table 8. Audiological Evaluation after Chemotherapy in Patients with Previous Hearing Loss (n-20)

Among the 52 patients with normal hearing 07/52 (13.46%) had developed moderate hearing loss and among the 20 patients with pre-existing hearing loss, 04 /20 (20%) patients had developed severe sensorineural hearing loss in this study.

Analysing the degree of loss of hearing according to the age group of patients in this study showed that there was more loss of hearing reported and observed in the age groups of 18 to 28 years and 29 to 38 years than in the elderly age groups 59 to 68 years and 69 to 78 years. The Air conduction thresholds were between 45 and 75 dB in patients aged 18 to 28 years, with bone conduction thresholds between 35 and 45 dB, PTA was between 45 to 55 dB, SDS between 60 to 70% and with absent POAE values (Table 9). Similarly, The Air conduction thresholds were between 30 and 50 dB in patients aged 29 to 38 years, with bone conduction thresholds between 30 and 35 dB, PTA was

between 35 to 45 dB, SDS between 65 to 75% and with absent POAE values.

Age Group	Air Conduction	Bone Conduction	PTA	SDS	DPOAE
18 to 28 Yrs.	45 to 70 dB	35 to 40 dB	45 to 55 dB	60 to 70%	Absent
29 to 38 Yrs.	35 to 50 dB	30 to 35 dB	35 to 45 dB	65 to 75%	Absent
39 to 48 Yrs.	30 to 45 dB	30 to 35 dB	30 to 40 dB	65 to 75%	Present, abnormal
49 to 58 Yrs.	30 to 45 dB	25 to 30 dB	25 to 35 dB	70 to 75%	Present, abnormal
59 to 68 Yrs.	25 to 30 dB	25 to 30 dB	20 to 25 dB	75 to 80%	Normal
69 to 78 Yrs.	25 to 30 dB	20 to 25 dB	15 to 20 dB	80 to 85%	Normal

Table 9. Loss of Hearing in Different Age Groups (n-52), (SDS: Speech Discrimination Score)

DISCUSSION

Among the numerous anti-neoplastic chemotherapeutic agents used, Cisplatin is known to produce ototoxicity (potential ototoxic agent). It is used singly or frequently used in multiple drug treatment protocols. The mode of action of Cisplatin is by generation of reactive oxygen species. The injury to cochlea takes place in all the three sub-regions of organ of Corti; stria vascularis, spiral ligament and spiral ganglionic cells. There is overload of reactive oxygen species in the cells of organ of Corti leading to depletion of cochlear antioxidant enzyme system (e.g. Superoxide dismutase - SOD, catalase - CAT, glutathione peroxidase – GSH - Px and glutathione reductase – GSH - R, that scavenge and neutralize the superoxides generated [(12)]. There is a wide range in the hearing loss caused by Cisplatin; as high as 91% to as low as 9%. In this study among 72 patients who completed chemotherapy with Cisplatin 47 were males and 25 were females with a male to female ratio of 1.88:1. Among them 15 patients had Head and Neck carcinomas, 13 had Bronchogenic carcinoma, 12 had stomach carcinoma, 09 patients had carcinoma cervix, 06 patients had carcinoma breast, 05 patients had peri ampullary carcinoma of pancreas, 4 patients had ovarian carcinoma, 04 had oesophageal carcinoma, 02 patients had had non-Hodgkin's lymphoma, 01 patient had Neuro-ectodermal tumour and 01 patient had malignant Brenner tumour. Hearing loss with Cisplatin chemotherapy is dose dependent.[13] The potential for ototoxicity increases with bolus administration and may be reduced by low infusion over a long time period. But dose limitation of Cisplatin is usually based on renal impairment. Cumulative dose exceeding 400 mg, concomitant use with other ototoxic medications, previous sensorineural hearing loss and renal dysfunction appear to be predisposing factors increasing the possibility of hearing loss.[14] In this study, audiological evaluation among the 72 patients before the commencement of chemotherapy showed 52 patients had normal hearing with Air thresholds ranging from 10 to 20 dB with a mean of 14.45 ± 1.05 dB, Bone thresholds ranging from 05 to 10 dB with a mean of 09.45 ± 0.35 dB. The pure tone average was ranging from 15 to 20 dB with a mean of 17.15 ± 1.75 dB. The speech discrimination score was 80 to 85%. The DPOAE values were present and normal in all the patients (100%). Tange et al reported that 8 of the 23 of their Cisplatin treated patients (34.78%), demonstrated significant auditory changes above 8000 Hz; hence inclusion of high frequency audiometry in monitoring these patients was advised.[15] Shulman et al[16] recommended assessing the cochlear and vestibular function before, during and at the completion of parental drug treatment whenever possible. In this study pre and post chemotherapy audiological evaluation was done meticulously. Sweetow et al[17] in their study demonstrated the changes in auditory function following completion of chemotherapy. Schell et al[18] prospectively tested a large group of patients who received either Cisplatin, cranial irradiation or both. They reported that there was significantly greater potentiating of ototoxicity, when both therapies done together, but hearing acuity was either not affected or minimally affected for irradiation only group. In this study analysing the degree of loss of hearing according to the age group of patients in this study showed that there was more loss of hearing reported and observed in the age groups than in the elderly age groups.

Air conduction thresholds were between 45 and 75 dB in patients aged 18 to 28 years, with bone conduction thresholds between 35 and 45 dB, PTA was between 45 to 55 dB, SDS between 60 to 70% and with absent POAE values (Table 9). Young patients tend to be more susceptible to audiological changes associated with Cisplatin.[19] Few studies have found the relationship between free circulating Cisplatin in plasma with time.[20-22] They found that Cisplatin infusion during afternoon and evening results in low plasma levels of free Cisplatin, and hence fewer side effects including ototoxicity. Measurement of correlation between time and plasma concentration is beyond the scope of this study. There are numerous otoprotection agents under research, includes aspirin, antioxidants, intratympanic dexamethasone, hyperbaric oxygen, ginkobiloba extract, diethyldithiocarbamate, lipoic acid, vitamin E and sodium thiosulphate. Ototoxicity monitoring is essential in obtaining a pathophysiological description of the ototoxic agent's effects and for keeping track of the changes over time. Ototoxic hearing change has a relatively predictable course of action as it preferentially affects the basal turn of the cochlea, its outer hair cells in particular (high-frequency limit of hearing) and progresses to the apical portion including lower speech frequencies. Ototoxic monitoring can be successful only when a fixed regimen is followed. This involves the education and coordinated effort of numerous health professionals (oncologist, ENT specialist, audiologist, clinical pharmacist, nurses) and also patients. Monitoring techniques should be considered based on their efficacy, sensitivity, and specificity. American Society of Hearing Association (ASHA) and the American Academy of Audiology (AAA) recommend that baseline assessment should include behavioural measures such as pure-tone audiometry (PTA) from 250 Hz to 8,000 Hz and high-frequency audiometry (HFA) from 9,000 Hz to 20,000 Hz, plus objective measures such as distortion product of Otoacoustic emissions (DPOAEs). In this study the ASHA guidelines were followed in audiological evaluation.

CONCLUSIONS

Among the 52 patients with normal hearing 07 / 52 (13.46%) had developed moderate sensorineural hearing loss and among the 20 patients with pre-existing hearing loss, 04 /20 (20%) patients had developed severe sensorineural hearing loss in this study. Hence Audiologic monitoring is important in patients undergoing Cisplatin chemotherapy and post-chemotherapy auditory monitoring is essential to rehabilitate the patients with sensorineural hearing loss.

Financial or Other Competing Interests: None.

REFERENCES

[1] Naunton RF, Ward PH. The ototoxicity of Kanamycin sulfate in the presence of compromised renal function. AMA Arch Otolaryngol 1959;69(4):398-399.
[2] Arslan E, Orzan E, Santarelli R. Global problem of drug-induced hearing loss. Ann N Y Acad Sci 1999;884:1-14.
[3] Cianfrone G, Pentangelo D, Cianfrone F, et al. Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. Eur Rev Med Pharmacol Sci 2011;15(6):601-636.
[4] Ruggiero A, Trombatore G, Triarico S, et al. Platinum compounds in children with cancer: toxicity and clinical management. Anticancer Drugs 2013;24(10):1007-1019.
[5] Landier W. Ototoxicity and cancer therapy. Cancer 2016;122(11):1647-1658.
[6] Knight KRG, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol 2005;23(34):8588-8596.
[7] Landier W, Knight K, Wong FL, et al. Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors and concordance of grading scales - a report from the Children's Oncology Group. J Clin Oncol 2014;32(6):527-534.
[8] Coradini PP, Cigana L, Selistre SGA, et al. Ototoxicity from Cisplatin therapy in childhood cancer. J Pediatr Hematol Oncol 2007;29(6):355-360.
[9] McKeage MJ. Comparative adverse effect profiles of platinum drugs. Drug Saf 1995;13(4):228-244.
[10] Bisht M, Bist SS. Ototoxicity: the hidden menace. Indian J Otolaryngol Head Neck Surg 2011;63(3):255-259.
[11] Rybak LP. Ototoxicity of loop diuretics. Otolaryngol Clin North Am 1993;26(5):829-844.
[12] Sivasankari L, Subramanian L. A study of cisplatin chemotherapy and hearing loss. Int J Otorhinolaryngol Head Neck Surg 2018;4(5):1297-1300.
[13] Helson DJ, Okonkwo E, Anton L. Cisplatinum ototoxicity. ClinToxicol 1978;13(4):469-478.
[14] Van der Hulst RJ, Dreschler WA, Urbanus NA. High frequency Audiometry in prospective clinical research of ototoxicity due to platinum derivatives. Ann Oto Rhinol Laryngol 1988;97(2 Pt 1):133-137.
[15] Tange RA, Dreschler WA, van der Hulst RJ. The importance of high tone audiometry in monitoring of ototoxicity. Arch Otolaryngol 1985;242(1):77-81.
[16] Shulman JB. Ototoxicity. In: Goodhill V, edr. Ear: diseases, deafness and dizziness. Hagerstown, MD: Harper and Row 1979: p. 691-704.
[17] Sweetow RW, Will TI. Progression of hearing loss following the completion of chemotherapy and radiation therapy: case report. J Am Acad Audiol 1993;4(6):360-363.
[18] Schell MJ, McHaney VA, Green AA, et al. Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol 1990;8:179-180.
[19] Weatherly RA, Owens JJ, Catlin FI, et al. Cis-platinum ototoxicity in children. Laryngoscope 1991;101(9):917-924.
[20] Hrushesky WJ. Circadian timing of cancer chemotherapy. Science 1985;228(4695):73-75.
[21] Hecquet B, Meynadier J, Bonneterre J, et al. Time dependency in plasmatic protein binding of Cisplatin. Cancer Treat Resp 1985;69(1):79-83.
[22] Rybak LP, Hussain K, Morris C, et al. Effect of protective agents against cisplatin ototoxicity. Am J Otol 2000;21(4):513-520.