NCRAR Workshop

Ototoxicity Early Identification & Monitoring

VA Rehabilitation Research & Development
National Center for Rehabilitative Auditory Research

Site by CDR Marketing Group

Outline

I. Learner Outcomes
II. Overview: Basic Principles
III. Tinnitus Monitoring
IV. Ototoxicity Monitoring in Adults
V. Objective Monitoring
VI. Ototoxicity Monitoring in Children
VII. Establishing Program

VI. Ototoxicity Monitoring in Children

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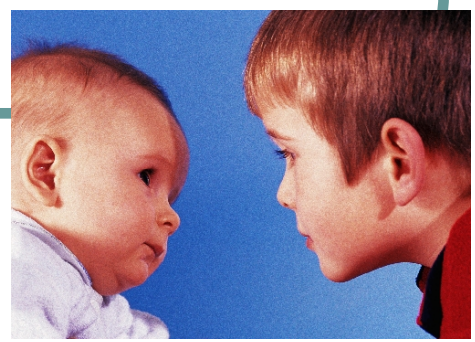
Doernbecher Children's Hospital



VA RR&D
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Background

- Incidence of ototoxicity in children treated with platinum chemotherapy: 26% to over 90%
  - Differences in dose of drug, time between courses, time of administration, cumulative dose
  - Differences in age
  - Definition of ototoxicity
  - Individual variability

Characteristics of platinum ototoxicity

- Hearing loss in the high frequencies initially.
- Hearing loss increases in severity and spreads to lower frequencies with continued treatment
- Platinum causes damage to stria vascularis, outer hair cells, and eventually inner hair cells
  - Blakely et al., Otolaryngology Head & Neck Surgery, 1993

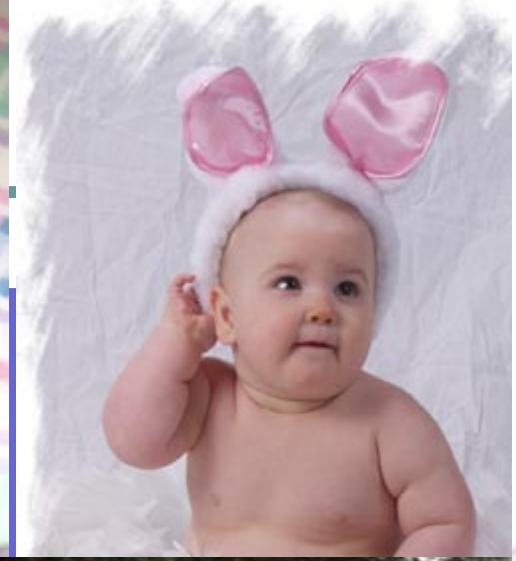
Factors that increase a child's risk for platinum ototoxicity

- Young age
- Cranial radiation before platinum chemotherapy.
- Cumulative cisplatin dose >400 mg/m2.
- Treatment with cisplatin and carboplatin.
- Use of aminoglycoside antibiotics (common), and/or loop diuretics during chemotherapy.
- Kidney disease/dysfunction.

- Li et al., Pediatric Blood and Cancer, 2004

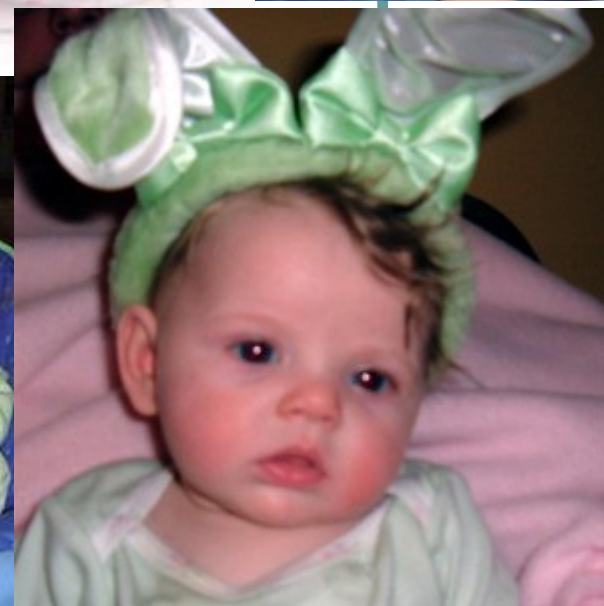
Why monitor for ototoxicity?

- Oncologist may be able to decrease platinum dose or delete platinum from treatment.
- Recommend habilitation for hearing loss if needed.
- Provide information to parents/teachers – children may not report difficulty hearing.







Consequences of High Frequency Hearing Loss

- Difficulty hearing/discriminating high frequency speech sounds (s, f, th, k, p, h, sh, ch).
- Difficulty hearing speech over distance and in noise.
- Difficulty hearing morphological markers of speech (plurals, tense).
- Delay in speech and language development in young children.
- Increased risk for difficulty in school.
  - Stelmachowicz et al, Archives Otolaryngology Head & Neck Surgery, 2004.

Need for Long-term Monitoring:

- 120 children treated with platinum chemotherapy were followed for a median 7 years after treatment.
- 37% treated with cisplatin and 43% treated with cisplatin and carboplatin had further deterioration of hearing (>20 dB).
- Progression seen in lower frequencies on follow-up.
- Hearing loss seen in children who did not show ototoxicity during treatment.

Bertolini et al., Pediatric Hematology and Oncology, 2004.

Ototoxicity Monitoring at DCH

- Baseline before the first platinum treatment:
  - Pure tone thresholds 500-8000 Hz.
  - Tympanometry.
  - Measurement of DPOAE's.
    - f2: 1500-10,000 Hz, L1/L2=65/55 dB SPL, f2/f1=1.22
  - Extended high frequency audiometry.

Monitoring Evaluations

- Before each platinum cycle:
  - Repeat pure tone thresholds 500-8000 Hz.
  - Tympanometry.
  - DPOAE’s.
  - Extended high frequency audiometry.
  - Bone conduction thresholds if significant threshold shift.

Long-term Monitoring

- Children without hearing loss at the end of treatment: 6 months and then annually for 3 years.
- Children with hearing loss: 3 months and then every 6 months.

Methods of Behavioral Evaluation

- 6 to 30 months: Visual reinforcement audiometry (with insert earphones whenever possible).
- 24 months – 6 years: Conditioned play audiometry.
- Over 6 years: Standard pure tone audiometry (6-20 years).

Methods of Behavioral Evaluation

- Tone evoked ABR
  - Used to estimate thresholds of hearing in children too young or too ill to provide reliable pure tone thresholds.
  - Pediatric sedation.
  - Thresholds measured for 500, 1000, 2000, 4000 Hz stimuli.
  - Measured down to threshold within 5 dB nHL.
  - ABR repeated if DPOAE's or behavioral responses indicate change in hearing.

Retrospective Study of Children Seen at DCH

- N=67
- 8 months – 20 years treated with cisplatin/carboplatin or both.
- Dose of cisplatin/carboplatin and treatment schedule varied depending on diagnosis.
- Monitored with conventional audiometry.
- Ototoxicity defined by ASHA criteria.

  - Gilmer Knight et al., Journal of Clinical Oncology, in press.

Results:

- 41/67 (61%) bilateral ototoxicity.
- Most children met ASHA criteria by 2nd or 3rd treatment.
- 17/41 children with ototoxicity referred for hearing aids.
- Children who had higher cumulative doses of cisplatin acquired more severe hearing loss.
- As a group, children treated for neuroblastoma had the most severe hearing losses (moderate-severe 3000-8000 Hz).

DPOAE's & Conventional Audiometry

- N=30 children (7 months to 20 years).
- 20/30 (67%) bilateral ototoxicity (ASHA criteria) in the conventional frequencies.
- Additional 4 with unilateral ototoxicity (left ear).
- 25/30 (83%) bilateral changes in OAE's.
- Additional 2 with unilateral decreases in OAE's (left ear).
- DPOAE's changed before pure tone thresholds.
- DPOAE's were decreased in every child who had ototoxicity in the conventional frequencies.

Extended high frequency audiometry and DPOAE's

- 15 children (5-20 years) had monitoring with pure tone audiometry 500-16,000 Hz and DPOAE's.
- 14/15 (93%) had bilateral ototoxicity by ASHA criteria in the EHF (and one in the right ear only).
- 10/15 (67%) bilateral changes in OAE's, (and 2 left only).
- 8/15 (53%) bilateral ototoxicity conventional frequencies, (and 2 left only).

Challenges:

- Cooperation, attention, poor response reliability when child is ill.
- Difficulty measuring EHF audiometry in children younger than 5 years.
- Middle ear pathology.
- Need for sedation to measure threshold ABR’s.
- Need for quiet child when measuring OAE’s.

Suggestions:

- Use a trained test-assistant.
- Schedule enough time to complete the evaluation.
- Measure high frequencies first (start at 8000 Hz).
- Have many interesting, quiet toys.
- Measure OAE’s in the child’s room during sleep, or following sedated procedure.

Case Study

- 8 year old female diagnosed with hepatoblastoma September 2004.
- Medical history: congenital grade 3 hydronephrosis and duplication anomalies of the left kidney. Corrective surgery at 9 months.

Chemotherapy Treatment:

- Vincristine, 5-Fluorouracil, Cisplatin
- Cisplatin dose
  - 100 mg/m2 over four hours every 3 weeks, 6 courses.
  - Target cumulative dose 600 mg/m2.

Baseline Evaluation

- Normal hearing sensitivity 250-8000 Hz.
- Normal DPOAE's 1500-5000 Hz. OAE's were reduced at 5900-10,000 Hz.
- EHF thresholds 30 dB SPL or lower 9000-16,000 Hz.

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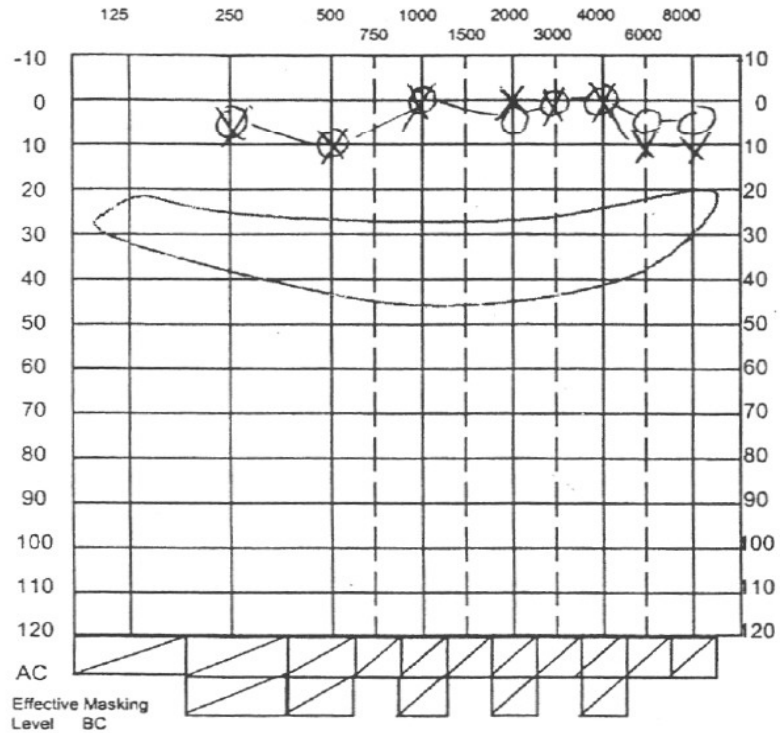
AUDIOMETRIC MEASUREMENT TEST

Stamp Patient Card Here

Date	9/9/04	Audiometer	IA AC-40	Audiologist: Natasha Carmichael, MS CCC-A
				Referral Source: Stacy Nicholson, MD
				Test Reliability: Good [X] Fair [ ] Poor [ ]

FREQUENCY IN HERTZ



Audiogram Key

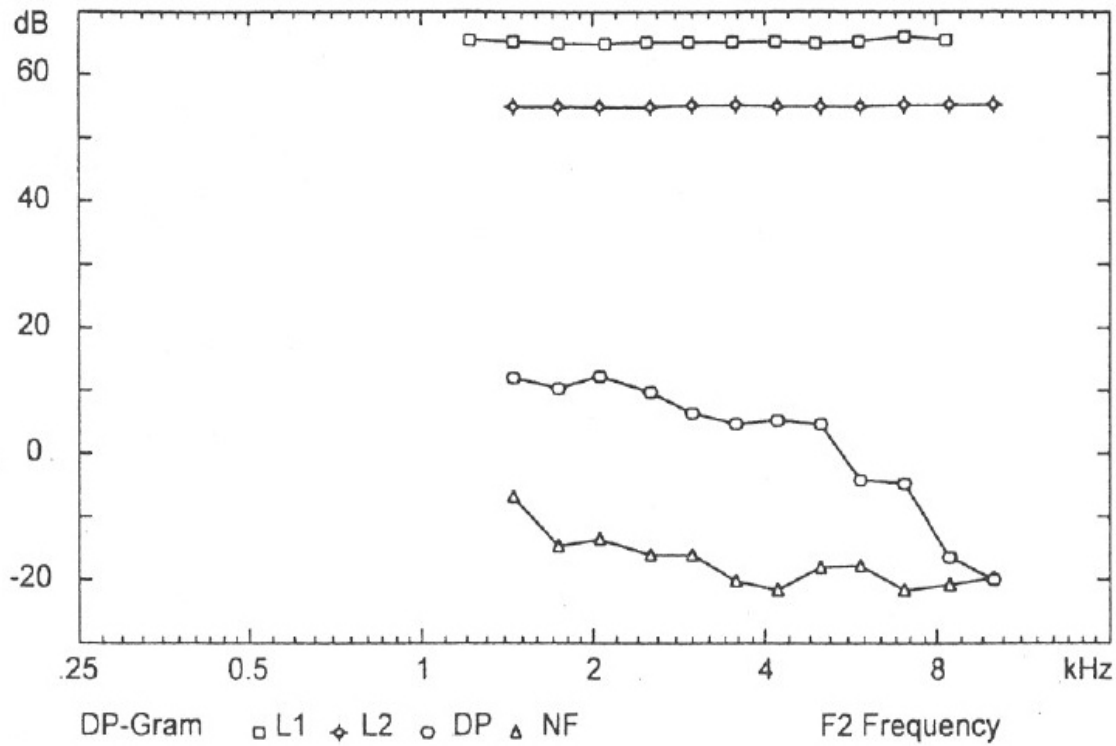
EAR	Unmasked AC	Unmasked BC	Masked AC	Masked BC	Sound Field Unaided	Sound Field Aided
R	O	<	Δ	[	S	A
L	X	>	□	]		
No Response - NR						
R	↙O	↘	↙Δ	↙[	S↘	A↘
L	X↘	↗	□↖	]↖		

Right:	PTA		SAL		SRT	0
	WRS	100	@	25dB		
	WRS		@			
Left:	PTA		SAL		SRT	0
	WRS	96%	@	25dB		
	WRS		@			
SF	PTA		SAL		SRT	
Unaided	WRS		@			
	WRS		@			
SF	PTA		SAL		SRT	
Aided	WRS		@			
	WRS		@			

BIO-LOGIC OTOACOUSTIC EMISSIONS (OAE) REPORT - Page 1 of 1

Patient:
Birthdat
ID:
Comment:

Ear: Right



Right: 09-Sep-04: -: 1.5-10 kHz Ototoxic Test: 04I09D03.OAE

BIO-LOGIC OTOACOUSTIC EMISSIONS (OAE) REPORT - Page 1 of 1

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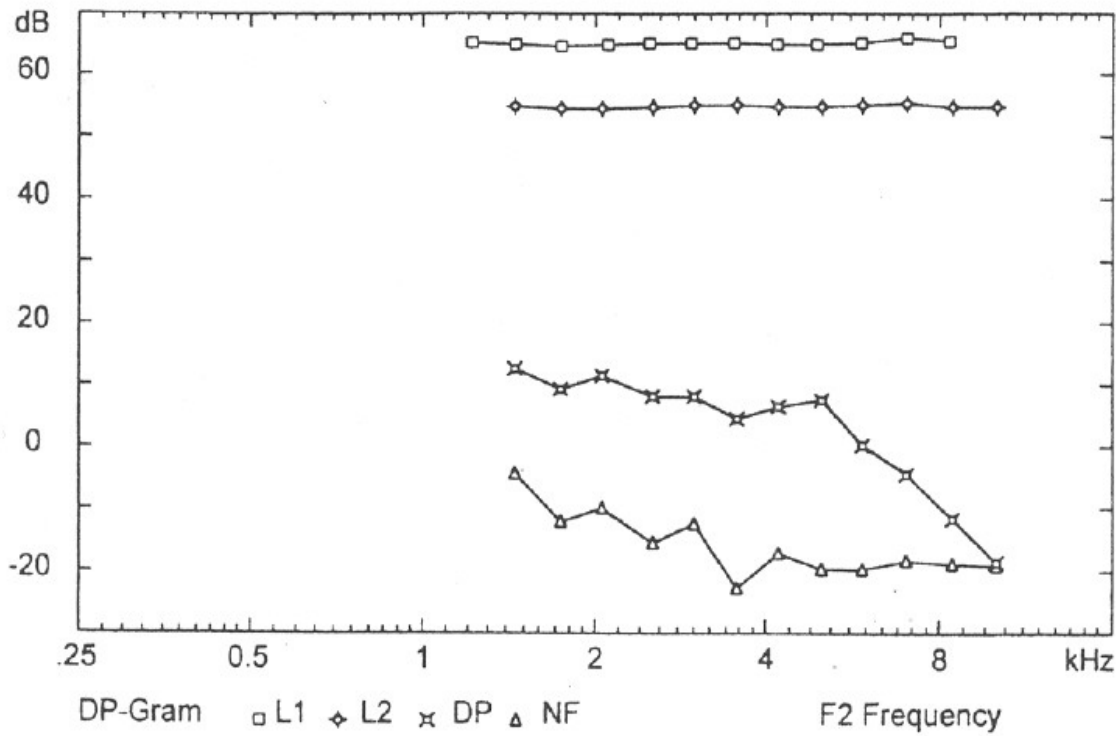
Birthdate:
ID:
Comment:

Ear: Left



Left: 09-Sep-04: -: 1.5-10 kHz Ototoxic Test: 04I09D02.OAE

Results (continued)

- Ototoxicity EHF after first cisplatin treatment.
- OAE's significantly reduced in the high frequencies after 2nd cisplatin treatment.
- Ototoxicity in speech frequencies after 2nd treatment.
- Cisplatin dose reduced 50% following 3rd cycle due to ototoxicity.

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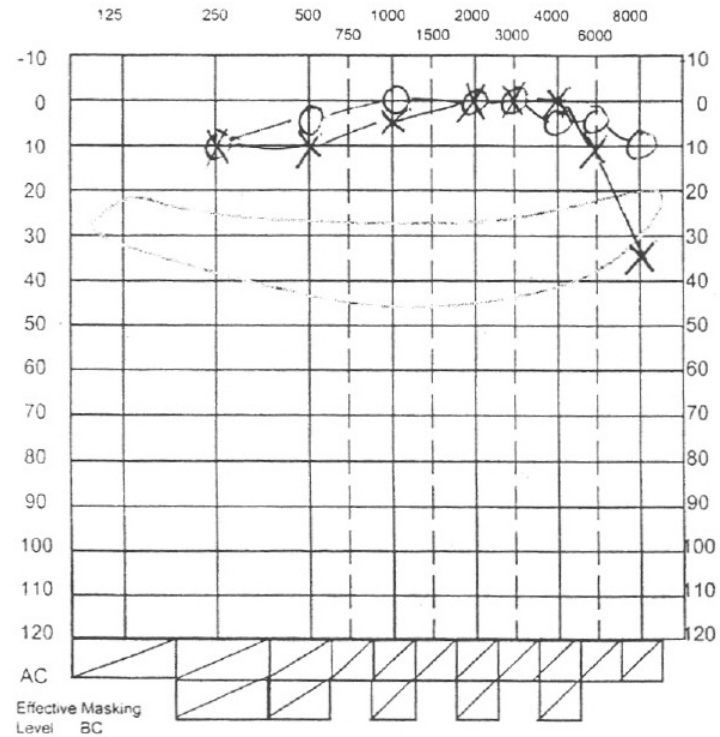
AUDIOMETRIC MEASUREMENT TEST

Stamp Patient Card Here

Date	9/27/04	Audiometer	IA AC-40	Audiologist: Natasha Carmichael, MS CCC-A
				Referral Source: Stacy Nicholson, MD
				Test Reliability: Good X Fair	Poor

FREQUENCY IN HERTZ



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EAR	Unmasked AC	Unmasked BC	Masked AC	Masked BC	Sound Field Unaided	Sound Field Aided
R	O	<	Δ	[	S	A
L	X	>	□	]		
No Response - NR						
R	O↓	↘	Δ↓	[↓	S↘	A↘
L	X↘	↘	□↘	]↘		

Right:	PTA		SAL		SRT	0
	WRS	100	@	25dB		
	WRS		@			
Left:	PTA		SAL		SRT	0
	WRS	96%	@	25dB		
	WRS		@			
SF	PTA		SAL		SRT	
Unaided	WRS		@			
	WRS		@			
SF	PTA		SAL		SRT	
Aided	WRS		@			
	WRS		@			

BIO-LOGIC OTOACOUSTIC EMISSIONS (OAE) REPORT - Page 1 of 1

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Birthdate:
ID:
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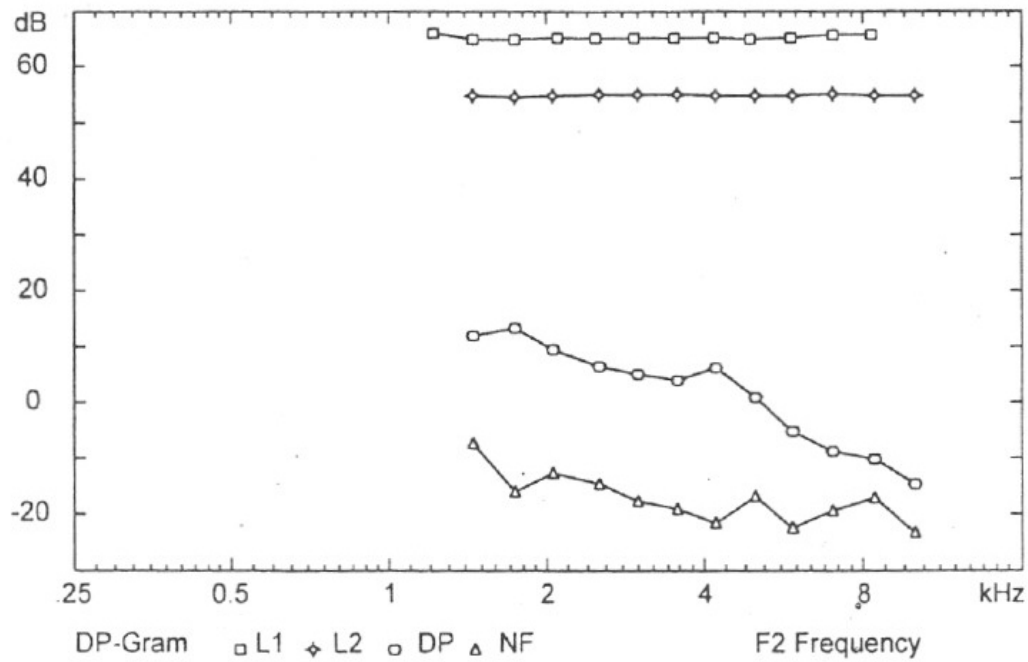
Ear: Right



Right: 27-Sep-04: -: 1.5-10 kHz Ototoxic Test: 04I27D01.OAE

BIO-LOGIC OTOACOUSTIC EMISSIONS (OAE) REPORT - Page 1 of 1

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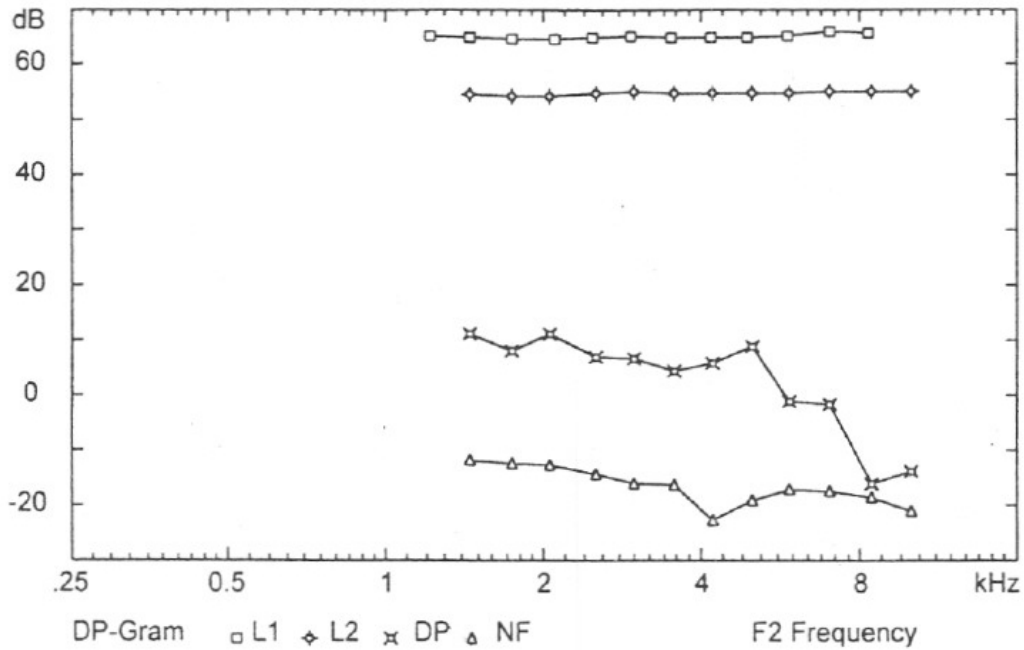

Left: 27-Sep-04: -: 1.5-10 kHz Ototoxic Test: 04I27D02.OAE

At Completion of Treatment:

- Mild to moderate bilateral high frequency hearing loss at 4000-8000 Hz.
- OAE's normal through 3000 Hz, absent in the high frequencies.
- Significant hearing loss in the EHF thresholds at all frequencies.

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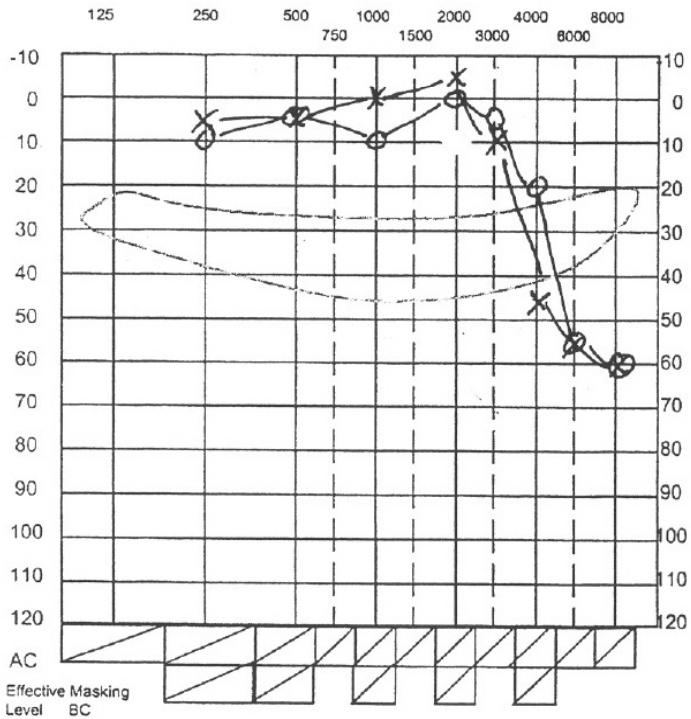
AUDIOMETRIC MEASUREMENT TEST

Stamp Patient Card Here

Date	2-23-2005	Audiometer	IA AC-40	Audiologist: Kristy Gilmer Knight, MS CCC-A
				Referral Source: Dr. Stacy Nicholson
				Test Reliability: Good X Fair Poor

FREQUENCY IN HERTZ



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L	X	>	□	]		
No Response - NR						
R	↙O	↘	Δ	[↙	S↘	A↘
L	X↘	>	□	]↘		

Right:	PTA		SA		SRT	5
	WRS	960%	@	30 dB HL		
	WRS		@			
Left:	PTA		SA		SRT	0
	WRS	100%	@	25 dB HL		
	WRS		@			
SF	PTA		SA		SRT	
Unaided	WRS		@			
	WRS		@			
SF	PTA		SA		SRT	
Aided	WRS		@			
	WRS		@			

BIO-LOGIC OTOACOUSTIC EMISSIONS (OAE) REPORT - Page 1 of 1

Patient:
Birthdate:
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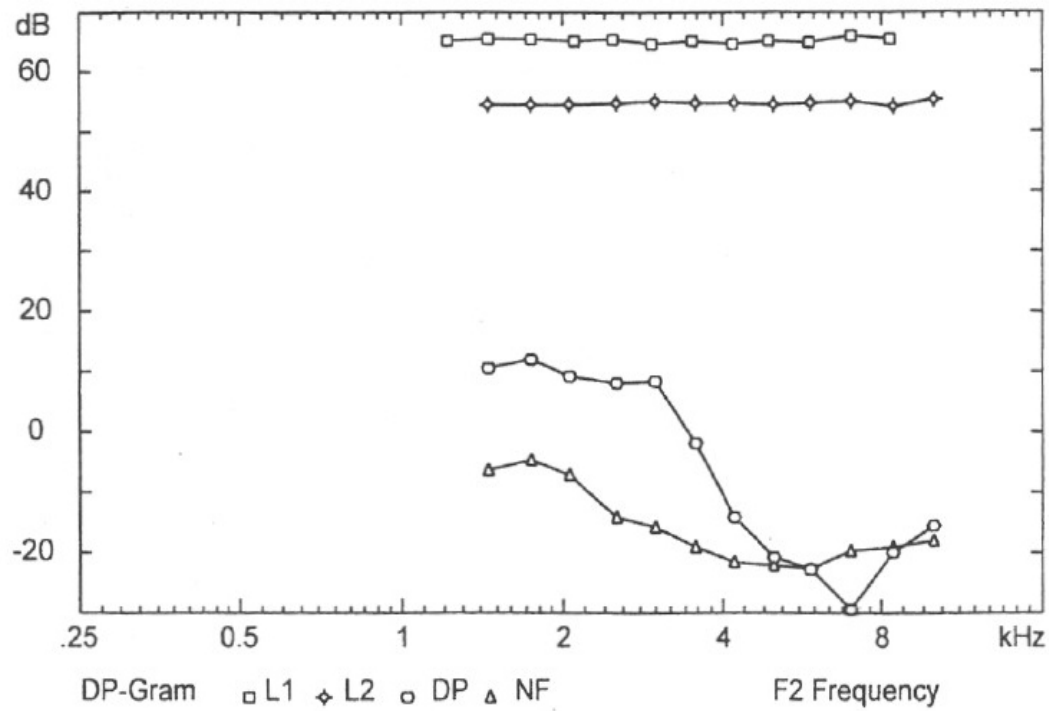
Ear: Right



Right: 23-Feb-05: -: 1.5-10 kHz Ototoxic Test: 05B23D03.OAE

BIO-LOGIC OTOACOUSTIC EMISSIONS (OAE) REPORT - Page 1 of 1

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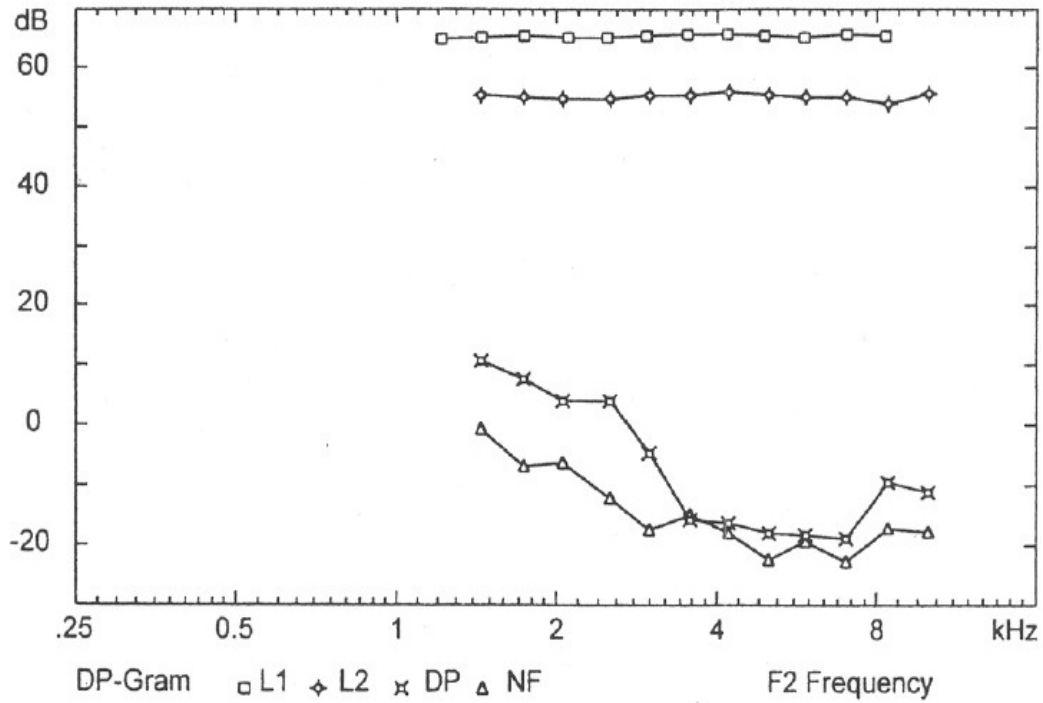
Ear: Left



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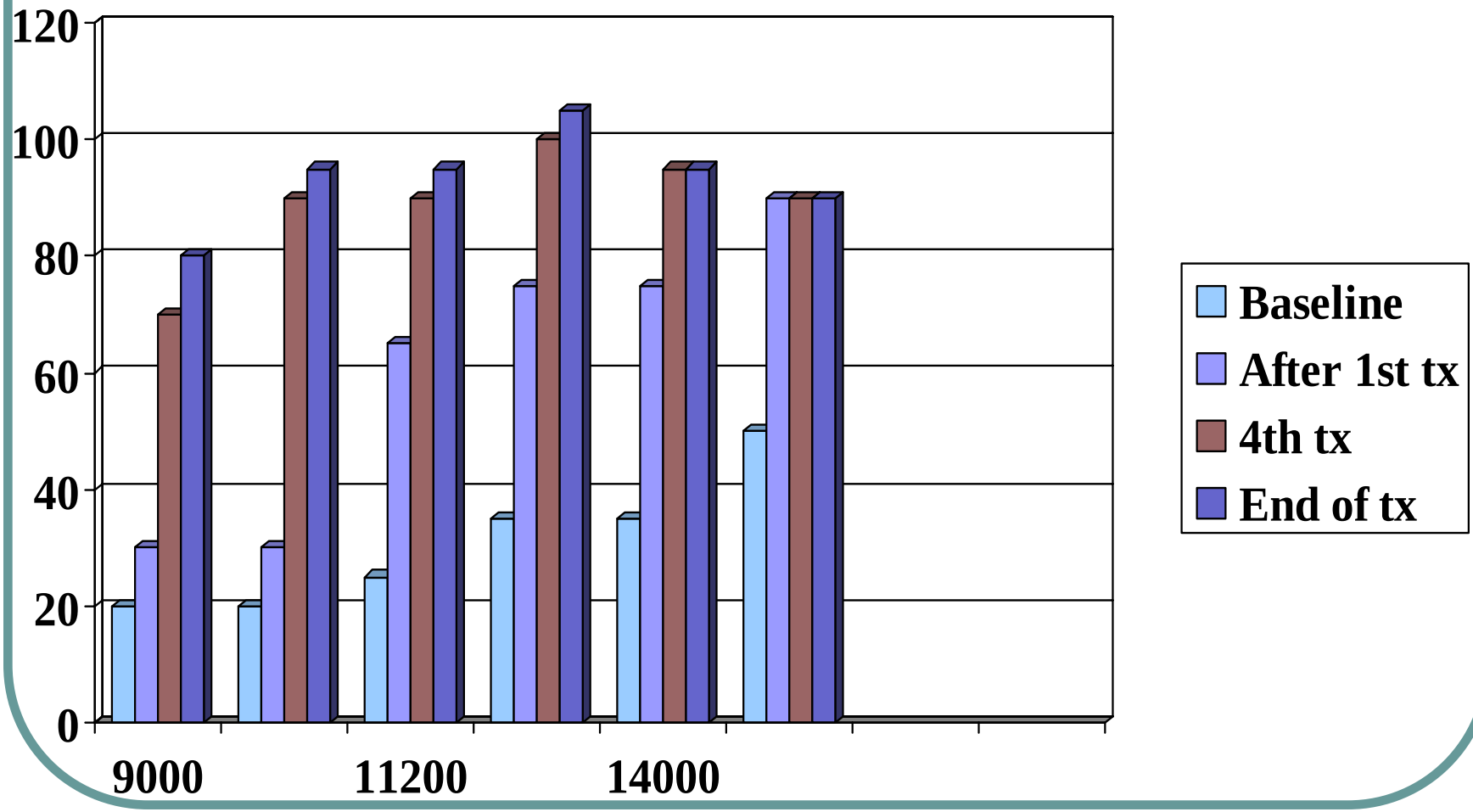
Extended high frequency thresholds



Follow-up

- Completed treatment in April 2005
- Attending 4th grade this fall.
- Preferential classroom seating and FM system recommended.
- Post-therapy audiologic evaluation in October 2005 to monitor for progression of hearing loss.