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Early changes of auditory brain stem evoked response after radiotherapy for nasopharyngeal carcinoma—A prospective study

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Abstract

A prospective study of the effect of radiotherapy for nasopharyngeal carcinoma on hearing was carried out on 49 patients who had pure tone, impedance audiometry and auditory brain stem evoked response (ABR) recordings before, immediately, three, six and 12 months after radiotherapy. Fourteen patients complained of intermittent tinnitus after radiotherapy. We found that 11 initially normal ears of nine patients developed a middle ear effusion, three to six months after radiotherapy. There was mixed sensorineural and conductive hearing impairment after radiotherapy. Persistent impairment of ABR was detected immediately after completion of radiotherapy. The waves I–III and I–V interpeak latency intervals were significantly prolonged one year after radiotherapy. The study shows that radiotherapy for nasopharyngeal carcinoma impairs hearing by acting on the middle ear, the cochlea and the brain stem auditory pathway.

Introduction

Radiotherapy (RT) for head and neck malignancies may have a detrimental effect on the nearby structures (Berge *et al.*, 1974; Manz *et al.*, 1979; Smith *et al.*, 1979; Elwany, 1985; Lam *et al.*, 1987; Qin *et al.*, 1988). The nasopharynx is separated from the brain stem only by the basiocciput. Radiation falling on to the brain stem in unavoidable during RT for nasopharyngeal carcinoma (NPC). There are reports of radiation-induced brain stem myelopathy or necrosis which usually occurs a few years after radiotherapy for nasopharyngeal carcinoma (Berge *et al.*, 1974; Manz *et al.*, 1979; Smith *et al.*, 1979). A constant pathology of radiation induced myelopathy is demyelination (Berge *et al.*, 1974). ABR is a sensitive and specific method to diagnose retrocochlear hearing loss (Selters and Brackmann, 1977), demyelination and other diseases of brain stem (Starr and Achor, 1975; Robinson and Rudge, 1977; Antonelli *et al.*, 1986). ABR can detect subclinical prolonged waves I–V IPLI in diabetic patients who have somatic neuropathy (Martini *et al.*, 1987). Hulcrantz (1985a, 1985b) and Anniko *et al.* (1987) also demonstrated prolonged waves I–V IPLI in the irradiated animals compared to non-irradiated ones indicating some type of disturbance in brain stem auditory pathway after RT. Nightingale *et al.* (1984) demonstrated statistically insignificant prolongation of waves I–V IPLI in a prospective study involving five patients who received radiotherapy for head and neck malignancy. In a prospective study, Kingston *et al.* (1986) found four children who developed abnormally large interaural difference of waves I–V IPLI after RT and chemotherapy for head and neck malignancy. Prolonged waves I–V IPLI were also

recorded from two NPC patients who had radiation-induced brain stem myelopathy (Lau *et al.*, 1988).

It is generally believed that irradiation damage to the nervous tissue is delayed in manifestation (Lampert and Davis, 1964). There is growing evidence that the electrophysiological changes after irradiation are immediate. Animal experiments showed disappearance of ABR and cochlear microphonic with degeneration of cochlear hair cells immediately after irradiation (Tokimoto and Kanagawa, 1985; Nagel and Schafer, 1984).

If there are any early physiological changes of the brain stem after radiotherapy for nasophargyngeal carcinoma, ABR is the most easily available and non-invasive tool for its detection. In order to analyze the effect of irradiation on the human brain stem, a prospective study was conducted on NPC patients who received radiotherapy as the primary treatment.

Materials and methods

Patients with NPC who were going to receive radiotherapy were included in this study. The following groups of patients were excluded: i) patients with ear diseases other than middle ear effusion (MEE); ii) patients who had pre-RT anti-cancer chemotherapy; and iii) patients who had involvement of cranial nerve by the tumour. All patients had clinical examination of their ears. Pure tone, impedance audiometry and ABR recordings were performed before and within one week, three, six and 12 months after RT. An Interacoustics AC4 pure tone audiometer calibrated to ISO standard was used. The pure tone audiometric tests were carried out inside a sound

TABLE I

CHANGES OF TYMPANIC MEMBRANES OF 49 PATIENTS WITH NASOPHARYNGEAL CARCINOMA 12 MONTHS AFTER RADIOTHERAPY (N = NUMBER OF EARS, MEE = MIDDLE EAR EFFUSION)

Before RT	n	12 months after RT	n
Normal	84	Normal	60
		Fibrotic	12
		Retracted	1
		Ventilation tube in situ	3
		MEE	6
		Perforation	2
		Total	84
MEE with ventilation tubes	14	Normal	6
		Fibrotic, intact	2
		Retracted	2
		MEE, recurrent	2
		Ventilation tube in situ	0
		Dry perforation	2
		Total	14

treated booth. The pure tone audiometer is calibrated annually by the Audiology Service, Arran Street, Hong Kong Government. Impedance was measured with an Interacoustics AZ7 impedance audiometer. In patients who had MEE before radiotherapy, ventilation tubes were inserted under local anaesthesia (Wei et al., 1987). The ABR was recorded after the insertion of ventilation tubes. At each follow-up session, the patients were examined clinically.

Radiation technique

Irradiation was given either by a Cobalt 60 machine or a linear accelerator producing 8 MV photons. Those patients with high cervical metastatic lymph nodes or oro-

pharyngeal involvement were treated with two lateral opposing faciocervical fields to irradiate the nasopharynx and neck in one volume during the initial phase of treatment. The plan was then changed to a three fields technique, the nasopharynx being irradiated with one anterior facial and two lateral opposing facial fields. For patients without cervical metastatic lymph nodes or oropharyngeal involvement, the whole course of treatment was given by three fields technique with one anterior and two lateral opposing facial fields. The neck was treated with a single anterior cervical field prophylactically.

Auditory brain stem evoked response technique

The ABR was recorded with Medelec MS92A signal averager. Clicks of alternating polarity generated by 100 μsec current from Medelec ST10 stimulator were presented to patients through TDH-49P earphone at a rate of 10/sec. Responses to 1024 clicks of alternating polarity at intensities of 60 dB SL were recorded. The analysis time was 10 ms during which period 1,000 data points were sampled. The contralateral ear was masked with broad band noise. Electrodes were placed on the vertex, the ipsilateral and contralateral mastoid processes, the last acting as the ground electrode. The skin was thoroughly cleaned with acetone before the application of electrode in order to keep the impedance of electrodes connection below 5 Kohm. The high pass filter was 200 Hz and the low pass filter was 2 Khz. ABR recording was done by one of the three audiometricians who was not aware of the detailed status of the patients regarding radiotherapy. Interpretation of the ABR wave latency and amplitude was made on-line. Vertex positive ABR waves were numbered from I to V (Jewett and Williston, 1971). Latencies were measured from the onset of the electrical pulse to the nearest 0.04 ms with the cursor. When subcomponents of waves were present, latency was measured to the peak with the largest amplitude. When the two subcomponents were equal, latency was measured to the peak of the second one. When the wave had an indistinct peak, latency was measured at the start of the downward deflection. Amplitude was measured from the positive peak to the subsequent negative trough. At least two tests were done at each setting to ascertain the reproducibility of the ABR.
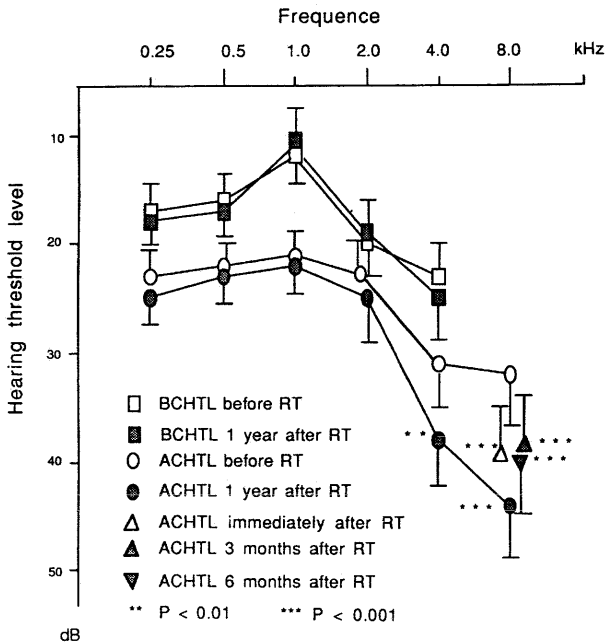

FIG. 1

Mean (SEM) of air and bone conduction pure tone hearing threshold level of 49 patients with NPC before and 12 months after radiotherapy (**P<0.01; ***P<0.001). BCHTL = Bone conduction hearing threshold level. ACHTL = Air conduction hearing threshold level.

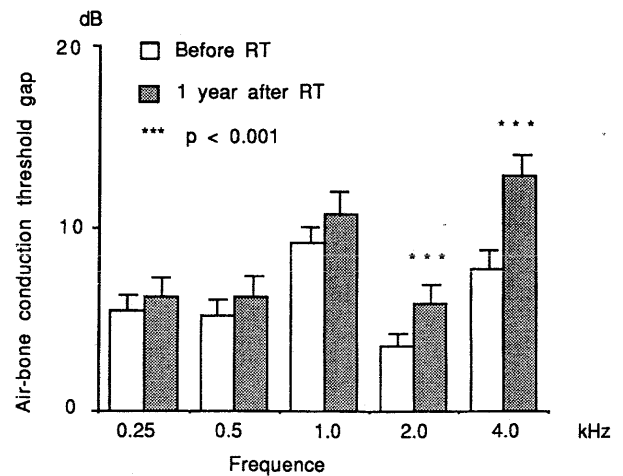
FIG. 2

Mean (SEM) of air and bone conduction threshold gap of 49 patients with NPC before and 12 months after radiotherapy (***P<0.001).

	Wave I	Wave II	Wave III	Wave IV	Wave V	Wave I–III IPLI	Wave I–V IPLI
Before RT Mean	1.64	2.72	3.81	4.96	5.67	2.17	4.04
SD	0.14	0.19	0.20	0.24	0.22	0.16	0.20
Range	1.3–1.94	2.42–3.36	3.48–4.29	4.3–5.32	5.24–6.20	1.90–2.59	3.64–4.40
Immediately Mean	1.74*	2.85***	3.94***	5.12	5.85**	2.21	4.10
SD	0.27	0.29	0.27	2.25	0.29	0.23	0.25
Range	1.39–2.54	2.36–3.14	3.44–4.99	4.68–5.62	5.20–6.86	1.86–2.92	3.68–4.80
3 months Mean	1.75*	2.85**	3.94***	5.07	5.85***	2.18	4.09
SD	0.22	0.26	0.24	0.28	0.24	0.19	0.25
Range	1.40–2.34	2.48–3.60	3.62–4.58	4.28–5.64	5.26–6.40	1.48–2.62	3.64–4.56
6 months Mean	1.73**	2.87***	3.95***	5.07***	5.84***	2.22**	4.11**
SD	0.21	0.24	0.23	0.23	0.24	0.18	0.23
Range	1.34–2.42	2.40–3.44	3.56–4.48	4.60–5.80	5.39–6.44	1.84–2.56	3.60–4.70
1 year Mean	1.69**	2.78**	3.93***	5.08***	5.81***	2.23**	4.12**
SD	0.20	0.23	0.25	0.23	0.22	0.17	0.21
Range	1.40–2.35	2.42–3.62	3.55–4.58	4.70–5.68	5.42–6.36	1.81–2.65	3.66–4.58

Wave peaks were identified if present in two of the three replications at approximately the same latency.

Statistical methods

Each patient underwent ABR recordings on five occasions during the study period of one year. The mean latencies and amplitudes of the two or three replications of the ABR waves during each investigation were used for statistical analysis. The amplitude of an ABR wave which disappeared was taken as zero. Because there was only one brain stem, the ABR data from one ear chosen randomly from each patient were used in analysis to avoid statistical duplication of the effect of irradiation on brain stem wave. In case of pure tone thresholds, middle ear compliance and pressure, the data from both ears were considered. Statistical significance was evaluated by Wilcoxon matched pair signed-rank test.

Results

Forty-nine patients (31 male and 18 female) had completed the study. The mean age was 43 years (range: 22 to 60).

The mean ±SD radiation dose delivered to the nasopharynx was 6409 ± 680 cGy. The estimated doses at the cochlea and the anterior surface of brain stem were 5892 ± 628 and 6287 ± 849 cGy respectively.

Before radiotherapy, eleven patients complained of tinnitus as a presenting symptom of NPC. In addition, four patients complained of hearing loss which was due to NPC. Twenty-four patients (49%) who did not have tinnitus before RT developed tinnitus during or after completion of RT. Fourteen of them (29 per cent) continued to complain of intermittent tinnitus 12 months after radiotherapy. Twenty-two patients (45 per cent) who did not complain of hearing loss before RT complained of it during or after completion of RT. In 15 of them (31 per cent) the complaints persisted 12 months after RT.

Changes in the middle ears

Ventilation tubes were inserted into 14 ears which had MEE before RT. All the ventilation tubes were extruded spontaneously within one year of RT. Two ears were left with dry central perforations at the myringotomy sites. Two ears had recurrent MEE after the ventilation tubes were extruded spontaneously. The changes in the tympanic membranes and middle ears 12 months after radiotherapy are listed in Table I. Of the 84 normal ears, 60 remained normal 12 months after RT. Eleven initially normal ears in nine patients developed MEE three to six months after RT (Table I). Five ears had ventilation tubes inserted. Three tubes remained in situ at the end of the study period. However, two ventilation tubes were extruded spontaneously four months after insertion resulting in a dry perforation of the tympanic membrane.

Changes in pure tone audiometry and impedance measurements after RT

The biggest impairment of hearing occurred at high frequency. The impairment of air conduction hearing threshold level (ACHTL) at 8 kHz was immediate (10 dB $P<0.001$) and persisted for 12 months (12 dB $P<0.001$) after RT (Fig. 1). There was no significant change in the bone conduction hearing threshold level (BCHTL) at the lower frequencies (0.25 to 4 kHz) throughout the study period. The BCHTL at 4 kHz was impaired by 2 dB ($P>0.05$). The air-bone gap at 0.25, 0.5, 1 kHz did not change significantly after RT (Fig. 2). However, at the end of one year the air-bone gap at 2 and 4 kHz increased by 3 and 5 dB respectively ($P<0.001$) (Fig. 2).

The mean ±SD of middle ear pressure (MEP) before RT was −52 ± 72 daPa. The MEP became more negative immediately after radiotherapy (−72 ± 74 daPa $P<0.01$). The negative shift of MEP was maximal 3

TABLE III
NUMBER OF EARS OF 49 PATIENTS IN WHICH WAVES I–III OR WAVES I–V INTERPEAK LATENCY INTERVALS (IPLI) WERE PROLONGED AFTER RT

	Prolonged I–III IPLI	Prolonged I–V IPLI
Immediately after RT	55	46
3 months after RT	51	55
6 months after RT	51	55
12 months after RT	59	68

TABLE IV

MEAN, SD AND RANGE OF AMPLITUDES (uV) OF ABR WAVES FROM 49 EARS (ONE EAR FROM EACH NASOPHARYNGEAL CARCINOMA PATIENT) BEFORE AND IMMEDIATELY, 3, 6 AND 12 MONTHS AFTER RADIOTHERAPY ($*P<0.05$, $**P<0.01$, $***P<0.001$)

	Wave I	Wave II	Wave III	Wave IV	Wave V
Before RT Mean	0.33	0.20	0.22	0.07	0.43
SD	0.15	0.13	0.10	0.08	0.12
Range	0–0.69	0.10–0.67	0.08–0.50	0–0.30	0.18–0.74
Immediately Mean	0.28*	0.17**	0.19*	0.05*	0.43
SD	0.15	0.12	0.11	0.06	0.15
Range	0–0.68	0–0.54	0–0.65	0–0.22	0–12–0.76
3 months Mean	0.24***	0.13***	0.17***	0.05*	0.41
SD	0.15	0.10	0.09	0.06	0.12
Range	0.00–0.62	0.00–0.37	0.02–0.45	0.00–0.23	0.09–0.65
6 months Mean	0.27***	0.13***	0.19**	0.05*	0.45
SD	0.14	0.09	0.08	0.07	0.12
Range	0.10–0.71	0.00–0.37	0.05–0.39	0.00–0.36	0.22–0.69
12 months Mean	0.27***	0.15*	0.19**	0.05**	0.45
SD	0.16	0.08	0.09	0.05	0.13
Range	0–0.74	0–0.33	0.04–0.49	0–0.19	0.21–0.74

months after RT (MEP $= -80 \pm 91$ daPa, $P<0.001$). It returned to its pre-radiotherapy level six months after radiotherapy (-64 ± 82 daPa $P<0.05$). The middle ear compliance decreased from pre-RT value of 0.86 ± 0.66 ml to 0.77 ± 0.60 ml 12 months after RT ($P<0.05$).

Changes of ABR after radiotherapy

ABR changes are listed in Tables II to VI. For the patient group the mean intensity was equivalent to 104 ± 6 dB and 106 ± 6 dB p.e. SPL before and one year after RT respectively. Immediately after radiotherapy, the absolute latencies of all ABR waves except wave IV were significantly prolonged ($P<0.05$). Twelve months later, latency of all ABR waves remained prolonged ($P<0.01$). The prolongation ranged from 0.05 to 0.14 ms. (Table II).

The number of patients with prolongation of waves I–III and waves I–V IPLI after RT increased with time. (Table III). The prolongation became statistically significant by six months ($P<0.05$) (Table II). The mean prolongation of the waves I–V IPLI was 0.08 ms one year after RT (Fig. 3).

The amplitudes of waves I, II, III and IV were reduced immediately after radiotherapy ($P<0.05$) and remained so one year later ($P<0.05$) (Table IV). Amplitude of wave V did not change throughout the study period.

Wave V was present in the ABR recording from all ears. On the other hand, wave IV was most vulnerable as it disappeared from six ears one year after radiotherapy (Table VI). In five ears wave I disappeared one year after radiotherapy. The number of patients' ears with abnormal latencies or IPLI slightly increased one year after RT (Table VI) (Chi-square test, p = n.s.).

Discussion

Impairment of hearing in the human ear after irradiation

TABLE V

NUMBER OF EARS OF 49 PATIENTS IN WHICH THE ABR WAVES WERE IDENTIFIABLE

	Wave Identifiable				
	I	II	III	IV	V
Before RT	96	95	96	72	98
Immediately after RT	93	88	95	63	98
3 months after RT	89	87	96	68	98
6 months after RT	90	86	95	68	98
12 months after RT	91	91	96	66	98

of head and neck malignancy has been reported in the literature. (Borsanyi et al., 1961; Dias, 1966; Leach, 1965; Moretti, 1976; O'Neill et al., 1979; Adler et al., 1985). In accordance with their findings, we found mixed sensorineural and conductive hearing loss after RT. The impairment was immediate in onset. It seems that hearing threshold level at high frequency is predominantly affected as the changes in hearing threshold level at low frequencies are insignificant. Although the BCHTL at 8 kHz was not performed it is most likely that the high frequency loss was due to damage of the cochlea or the auditory pathway. This is consistent with animal experiments which showed destruction of the outer hair cell of the basal coil after irradiation of the cochlea (Tokimoto and Kanagawa, 1985; Bohne et al., 1985). Generalized loss of hair cells and degeneration of spiral ganglion cells in lower basal were also found in irradiated human temporal bone (Schuknecht and Karmody, 1966).

In another study the BCHTL at 4 kHz was impaired after irradiation (Borsanyi et al., 1961). However, this sort of change is not significant in our study. It is possible that the impairment of BCHTL at 4 kHz will be more pronounced in longer follow-up because some of the effect of irradiation is delayed in onset (Moretti, 1976).

The enlarged air-bone conduction threshold gap at 2 and 4 kHz and the reduction of MEC probably indicated the structural change of the middle ear induced by irradiation (Gyorkey and Pollock, 1960; Borsanyi et al., 1961; Dias, 1966; O'Neill et al., 1979; Kveton and Sotelo-Avila, 1986). Degeneration of auditory nerve fibre after irradiation has been demonstrated in animal experiment (Bohne et al., 1985). However, little is known about the retro-

TABLE VI

NUMBER OF EARS IN 49 PATIENTS WITH LATENCY OR IPLI THAT EXCEEDED THE CORRESPONDING UPPER LIMIT OF NORMAL, BEFORE AND ONE YEAR AFTER RT

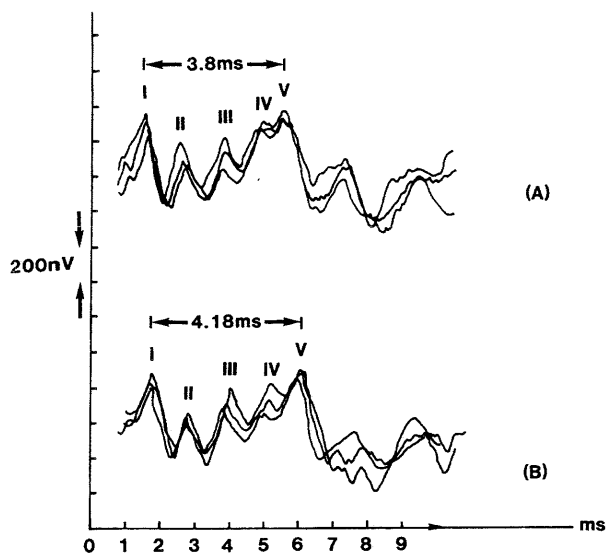| ABR wave	Before RT	One year after RT
Wave I	4	6
Wave II	5	6
Wave III	5	10
Wave IV	3	7
Wave V	3	6
Wave I–III IPLI	4	8
Wave I–V IPLI	4	6

Chi-square test, p = n.s.

FIG. 3

ABR of the right ear from one patient with NPC before (A) and 12 months after irradiation (B). The interpeak latency interval was prolonged.

cochlear element in radiation induced hearing loss in human. The prolongation of IPLI in our study confirmed the presence of a small retrocochlear element in radiation induced hearing loss in human.

The latency of manifestation of nervous tissue damage following radiotherapy for extra cranial malignancy ranges from six months to 14.3 years (Glass et al., 1984; Berger and Bataini, 1977). However, there is growing evidence that the electrophysiological changes after irradiation of the auditory system are immediate in onset (Tokimoto and Kanagawa, 1985; Nagel and Schafer, 1984). Our study found that the prolongation of latencies of all ABR waves except wave IV was already evident immediately after RT. The prolongation of IPLI reached statistically significant level six months after radiotherapy (P<0.01).

The radiation induced pathophysiological changes of the auditory system starting from the Eustachian tube to the brain stem have been documented. These changes must have some effect on the ABR. The damage of the cochlea hair cells may lead to prolongation of wave I and reduction in its amplitude. However, the radiation induced middle ear changes, e.g. fibrosis, MEE could have the same effect on ABR. The air bone conduction threshold gap at 2 and 4 kHz was increased by 3 and 5 dB respectively one year after RT. At the same time the mean click intensity employed one year after RT was increased by 2 dB. Probably the click intensity arriving at the inner ear was slightly diminished one year after RT. This would shift all the ABR waves to the right. However, such a slight decrease in the click intensity would have minimal effect on the IPLI. Therefore the prolongation of IPLI is due to the effect of irradiation on the brain stem auditory pathway. The above assumption is made because it is well known that irradiation of head and neck malignancies can lead to brain stem myelopathy or necrosis.

Conclusion

This study shows that radiotherapy for nasopharyngeal

carcinoma impairs hearing by adversely affecting the middle ear, the cochlea and brain stem auditory pathway. The early symptom of this irradiation damage is tinnitus. Other otological changes include the development of middle ear effusion, fibrotic changes of tympanic membrane and reduction of middle ear compliance. The hearing impairment is a mixed sensori-neural and conductive one. The significant changes of the ABR one year after RT include prolongation of latency of all ABR waves, reduction in amplitude of waves I, II, III, IV, and prolongation of waves I–III and I–V IPLI. This last change confirmed the presence of a small retrocochlear element in radiation induced hearing loss.

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