Changes in the Averaged Evoked Potentials (AEP) of the Patients with Brain Tumors during Therapeutic X-Irradiation

Takeru Minamisawa, Takehiko Tsuchiya, Hideo Eto and Goro Yamamoto*
Division of Radiation Hazards, National Institute of Radiological Sciences

放射線治療中の脳腫瘍患者の誘発電位の変化について

放医研障害基礎研究部
南沢　武，土屋　武彦，江藤　秀雄，*山本　五郎

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X線照射治療のため本研究所病院部に入院した10名の脳腫瘍患者（主として脳下垂体腫瘍）について，放射線照射による平均誘発電位（ＡＥＰ）の変化を研究した．1回50～250R，週4～5回，全線量2,450～5,050Rを脳腫瘍に照射した．3秒に1回の頻度で，合計200回光刺激を与え，その誘発電位を後頭部から記録し，CAT (Computer of Average Transients) で加算，平均し，ＡＥＰとした．ＡＥＰの記録は，初回照射時，線量増加時（1回の）,最終回照射時各々の直前，直後，2，5，24時間後および照射終了数十日後に行なつた．

ＡＥＰは潜時約30 msec 後の数個の波からなつており，その大きさ，頂点潜時は個体により異なつていた．Ⅳ，Ⅴ，Ⅵの波は大部分の個体から記録されたので，この三つの波についてその大きさの変化を検討した．(1) 初回照射によるＡＥＰの変化；50～150R照射2，5時間後，大部分の個体の三つの波は減少し，24時間後では元に戻らなかつた．線量増加時の場合も同様の傾向を示した．(2) 蓄積線量との関係；線量が増加するにつれてこれらの波は減少する傾向を示した．(3) 照射終了後の変化；照射終了後の値は一定の傾向を示さなかつた．以上の結果は，分割照射における線量の蓄積は放射線による脳幹の活動性の低下に対して蓄積的に作用するものと考えられる．

Abstract

Effects of fractionated X-irradiation on the averaged evoked potentials (AEP) to photic stimulation in ten patients with brain tumors were studied. Doses of 2,450 to 5,050 R, fractionated into 50 to 250 R per day, 4 to 5 times per week, were administered to the brain tumors. Two hundred evoked potentials were averaged in the CAT 400B.

Seven wave components, most particularly IV, V and VI, were observed in the first 200 msec of the AEP in the waking subjects. Three components (IV, V and VI) of the AEP of six subjects decreased in amplitude immediately after initial irradiation with 50 to 150 R. These components remained grossly unaltered for 24 hours after exposure. Their amplitude in most subjects gradually decreased during the

*Hospital, National Institute of Radiological Sciences. Present adress: Inoue Hospital, Chiba-shi.
*病院部：現在，井上病院（千葉市）

course of the radiation therapy. Changes in the AEP after the end of irradiation were investigated in three subjects. No consistent patterns were found.

Introduction

There have been many reports on physiological changes in the central nervous system after substantially lower doses of irradiation than those required to produce detectable structural damage[8)10)12)]. Caster and Armstrong[1)] detected EEG changes in rats following 700 R X-irradiation. We have reported a decrease in the visual evoked potential after X-irradiation of 250 to 1,000 R in rabbits[16)17)].

Ionizing radiations are widely used for treatment of brain tumors. We had recently the opportunity to record the EEG of patients who were treated with X-rays for brain tumors. In the past decade computer techniques have been developed which make it possible to dissect out from total EEG activity the response to specific stimuli. The visual evoked potentials have been studied most extensively as the response to a specific stimulus. In this paper we described changes in the averaged evoked potentials (AEP) to photic stimulation of the patients with brain tumors during fractionated therapeutic X-irradiation.

Methods

Ten patients with brain tumors served as subjects for this experiment. Seven of the patients suffered from hypophyseal tumor. The subject was seated in an electrically shielded, sound-deadened and darkened room. The head of each subject was measured and fitted with silver disc electrodes attached with bentonite paste. The electrodes were placed bilaterally at O_1, O_2, P_3 and P_4 according to the international 10–20 system. An ear-ground lead was used for referential recording. The EEG and the photic evoked potential were amplified by an electroencephalograph (Nikkor, ME-40D). Two hundred evoked potentials were averaged in the CAT 400B (Computer of Average Transients) at analysis time of 1 sec, and the AEP were recorded photographically. Flashes were presented at a frequency of 0.3 c/sec to both eyes by a photic stimulator (Nikkor, ME-IPS). The lamp was placed 100 cm in front of the subject's eyes. The AEP were taken before irradiation and immediately, 2, 5 and 24 hours after initial and final irradiation. The recordings were repeated each time the therapeutic dose was increased, according to the same schedule that was employed after intial irradiation. The AEP of some subjects were also recorded several months after the end of exposure. Doses of 2,450 to 5,050 R, fractionated into 50 to 250 R per day, 4 to 5 times per week, were administered to the brain tumors. The field of the radiation included a part of the reticular formation. The clinical data and recording schedule of the AEP in ten patients are summarized in Table 1.

Results

Seven wave components were observed in the first 200 msec of the AEP in the waking subjects. The peak latency of these components before irradiation differed from subject to subject, as is shown in Table 2. Componets I, II and III could be identified only in case 4 and 9, whereas component IV was taken from all subjects. The AEP of cases 4 and 8 did not have component V, and component VI was not observed in cases 7, 9 and 10. It was very difficult to decide each peak latency of the components of case 9, because these were very small and curved. Recordings of case 1 were begun when the first increased dose was administered. We employed only components IV, V and VI for the present study. The amplitude

Table 1. Clinical data and recording schedule of the AEP in ten patients.

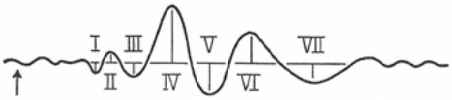
Case Sex Age	Recordings of the Averaged Evoked Potentials Date Single Dose (R) Cumulative Dose (R)					Days after Irradiation	Portion of Irradiation Field of Irradiation (cm)	Source Direction
	I	II	III	IV	End of Irradiation Total Dose (R)			
No. 1 Female 39		Nov. 29 100 250		Dec. 19 200 3,300	Dec. 26 4,700	Dec. 27	Head 6 × 10	6 MeV L & R
No. 2 Male 54	Jan. 9 50 0	Jan. 13 100 200	Jan. 20 200 1,000	Feb. 10 250 4,400	Feb. 10 4,650	Feb. 15 Mar. 18 May 2	Hypophysis 7 × 7	6 MeV L & R
No. 3 Male 74	Feb. 16 100 0			Mar. 7 200 2,250	Mar. 7 2,450	Mar. 14	Hypophysis 6 × 6	^{60}Co Rotation
No. 4 Female 46	Mar. 1 50 0		Mar. 10 150 750	Mar. 31 250 4,400	Mar. 31 4,650	Apr. 27 May 30 Jul 4	Hypophysis 6 × 6	6 MeV L & R
No. 5 Female 14	Mar. 13 50 0		Mar. 28 200 1,200	Apr. 20 250 4,250	Apr. 20 4,500	Apr. 22 May 28	Hypophysis 5 × 5	6 MeV L & R
No. 6 Male 33	Apr. 18 50 0		May 13 150 1,050	May 26 200 4.650	May 27 5,050	Jul 4 Oct. 3	Hypophysis 5 × 5	6 MeV L & R
No. 7 Male 15	Apr. 21 50 0		May 9 150 1,200	June 2 200 4,800	Jun. 2 5,000		Head 7 × 5.5	6 MeV L & R
No. 8 Female 9	Apr. 26 50 0			June 2 200 4,050	Jun. 3 4,450	Jul 11 Ju 26	Head 4 × 4	^{60}Co
No. 9 Female 46	May 11 50 0			June 19 200 4,800	Jun. 19 5,050	Jul 25	Hypophysis 5 × 5	6 MeV L & R
No. 10 Female 33	May 17 50 0		May 31 200 1,200	Jun. 26 250 4,800	Jun. 26 5,000	Jul 25 Oct. 3	Hypophysis 5 × 5	6 MeV L & R

of these components was measured from base line to peak.

Effects of initial irradiation

The changes in the amplitude of components IV, V and VI of the AEP during the 24 hours after initial irradiation of 50 R or 100 R are shown in Table 3 and Fig. 1. All components of the AEP, except in cases 4 and 10, decreased in amplitude immediately after irradiation. These components remained grossly unaltered for 24 hours after exposure. Component V of case 5 dropped to about one-third of control value in amplitude 5 hours after irradiation and IV of case 7 decreased by a half, but all components of most

Table 2. Schematic drawing of the AEP and peak latency (in msec) of seven components of the AEP in ten patients.



Case \ Component	I	II	III	IV	V	VI	VII
1			75	100	120	172	197
2				105	132		
3				87	107	142	
4	50	60	90	123		195	
5	52			126	147	177	
6				97	137	167	
7	57			87	102		
8				85		175	
9	50	65	70	97	117		
10			70	97	117		

Table 3. Changes in the amplitude of components IV, V and VI of the AEP during the 24 hours after initial irradiation. a) Component IV. b) Component V. c) Component VI. The value before irradiation is shown as 100%

a)

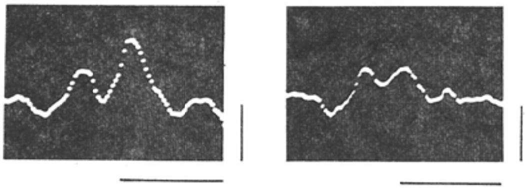
Case	Dose (R)	Before Irradiation	After Initial Irradiation (hours) 0	2	5	24
3	100	100		90.2		81.7
4	50	100	153.3	120.3	167.2	130.0
5	50	100		85.7		90.5
6	50	100	96.6	112.1	91.4	81.9
7	50	100	51.2		45.7	52.7
8	50	100			89.8	80.3
10	50	100				113.6

b)

Case	Dose (R)	Before Irradiation	After Initial Irradiation (hours) 0	2	5	24
3	100	100		83.3		95.8
5	50	100			31.3	
6	50	100	93.1	100.9	69.8	90.5
7	50	100	85.1			
10	50	100				222.2

c)

Case	Dose (R)	Before Irradiation	After Initial Irradiation (hours) 0	2	5	24
3	100	100		72.7		89.1
4	50	100	108.0	130.0	126.0	134.0
5	50	100		71.4	74.5	69.4
6	50	100	86.0	94.2	92.6	88.4
8	50	100			77.4	75.0



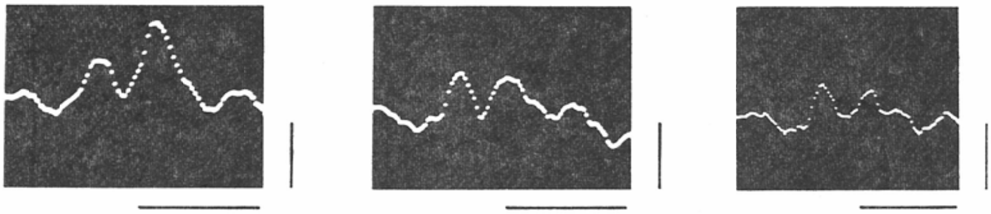
a) b)

Fig. 1, Changes in the AEP after initial irradiation with 50 R. a) Before irradiation. b) Five hours after irradiation. Calibration: 100 msec, 10 μV.

subjects remained at approximately 70–90% of control. Although the exact value could not be taken from case 2 because an artifact, both IV and V showed a tendency for amplitude to decrease after exposure. On the contrary, all components of cases 4 and 10 increased in amplitude after irradiation. The changes in the three components of the AEP observed during the 24 hours after the first increased dose irradiation were fairly similar to those of initial exposure.

Effects of cumulative dose

The changes in the amplitude of components IV, V and VI of the AEP during the course of therapy with repeated doses are shown in Figs. 2 and 3. All components of all of the subjects except case 4 generally decreased in amplitude with repeated until final exposure. The amplitude of IV and VI of cases



a) b) c)

Fig. 2. Changes in the AEP during fractionated irradiation. a) Before irradiation. b) One day after irradiation with 1,200 R. c) One day after irradiation with 4,800 R. Calibration: 100 msec, 10 μV.

3 and 8 and VI of case 6 showed a slight decrease during irradiation treatment. Component IV of cases 1 and 10 gradually decreased in amplitude with repeated dosage and reached about 50% at the end of therapy. The amplitude of component IV of cases 2 and 7 declined rapidly, followed by little change there after. To repeat, subjects showed considerable individual differences in the manner in which their AEP were affected by the X-irradiation.

Delayed effects of fractionated irradiation

The changes in the amplitude of components IV, V and VI of the AEP during the 7th through the 130th days after the end of therapy are shown in Table 4. The amplitude of all components of case 3, and both IV and V of case 5, which showed the decreased value at the final irradiation day, exceeded control level on the 7th and the 38th days after final exposure, respectively. On the other hand, the amplitude of all components of case 6 and VI of case 5 remained below control through the 38th day after exposure.

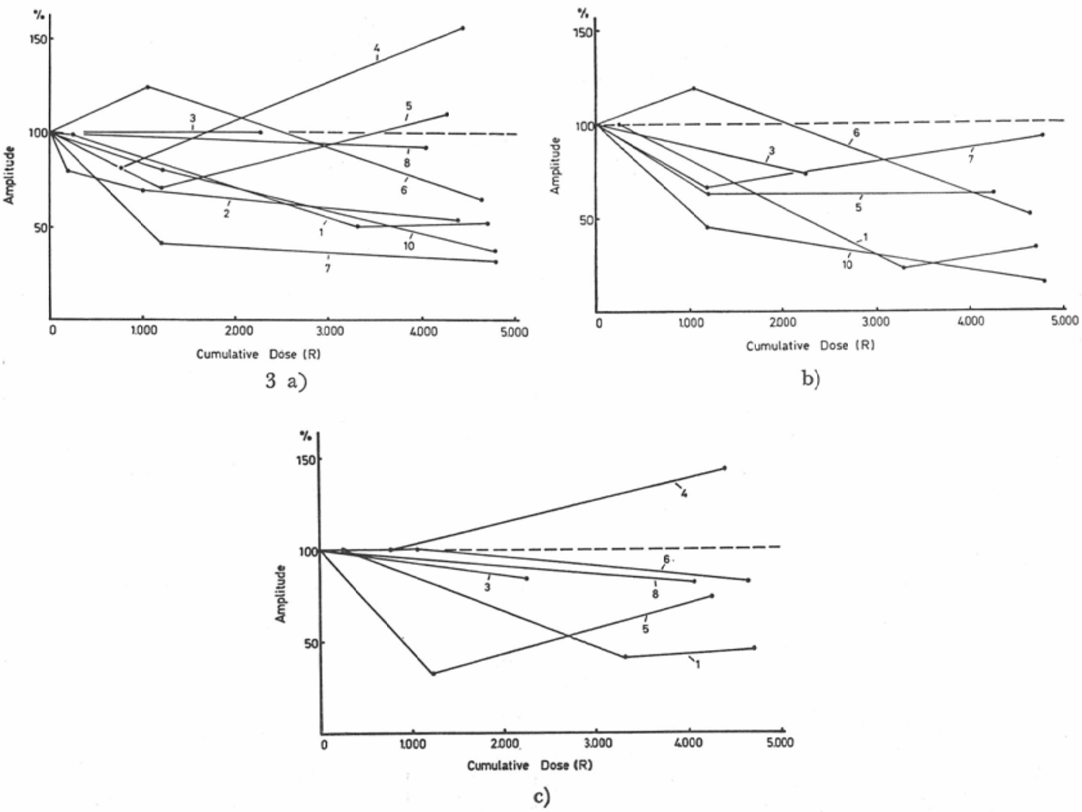


Fig. 3. Changes in the amplitude of components IV, V and VI of the AEP during fractionated irradiation. a) Component IV. b) Component V. c) Component VI. The value before irradiation is shown as 100%.

In case 6, the value on the 130th day was very similar to that observed on the 38th day.

Discussion

Effects of initial irradiation

The findings of the present study are in agreement with previous observations[16)17)] that in rabbits the visual evoked potential decreased after X-irradiation of 250 to 1,000 R. Grigor'yev[5)] also reported that the strength of the photic EEG response was decreased immediately after 50 to 100 R of therapeutic X- or gamma-irradiation. Changes of the early response of the visual cortex after exposure of 200 to 1,200 R have been reported by several investigators[3)11)18)]. According to Monnier and Hölsi[18)], the early response decreased in latency and in culmination time after exposure. This early response is considered to be identical with the primary response described by Cigánek[2)], who assumed that the primary response had the character of a potential produced by a specific pathway, and that the secondary response consisted of potentials produced by non-specific pathways. A close relationship between the level of reticular activity and the amplitude of the secondary response of the visual cortex has been reported by Fuster and Docter[4)], and Massopust and Wolin[15)]. Components IV, V and VI in this experiment, the visual evoked potential of previous papers[16)17)], all appear to be homologous to the secondary response of Cigánek[2)]. In this experiment,

Table 4. Changes in the amplitude of components IV, V and VI of the AEP during the 7th through the 130th days after final irradiation. a) Component IV. b) Component V. c) Component VI. The value before irradiation is shown as 100%.

a)

Case	Before Irradiation	Final Irradiation Day	After Final Irradiation days	
3	100	100.0	7	180.4
5	100	114.3	38	120.4
6	100	65.5	38	83.6
6	100	65.5	130	82.7

b)

Case	Before Irradiation	Final Irradiation Day	After Final Irradiation days	
3	100	72.9	7	112.5
5	100	62.5	38	118.8
6	100	62.1	38	78.3
6	100	62.1	130	72.4

c)

Case	Before Irradiation	Final Irradiation Day	After Final Irradiation days	
3	100	83.6	7	131.8
5	100	53.1	38	50.0
6	100	81.0	38	72.2
6	100	81.0	130	98.3

the field of the radiation included the reticular formation. From these considerations, it appears that the decrease of the amplitude of the AEP in this experiment may be related to the changes of the activity of the reticular formation.

Effects of cumulative dose

Some psychological investigators reported that repeated irradiation had cumulative effects on the central nervous system[13]. The present study indicating that the three components of the AEP showed a tendency to decrease in amplitude as a function of repetitive irradiation supports that conclusion. Håkansson *et al.*[7] demonstrated that during fractionated irradiation treatment following operation for malignant cerebral tumors, the cerebral electrical activity in the slow frequency range increased, even in that part of the brain that was not influenced by direct irradiation. Haley[9] also reported that in cats brains irradiated with 50 R per week developed sporadic 4 to 5 cps activity immediately after the first 50 R dose and that this activity continued until sacrifice, by which time the animal has received a total of 1,350 R. However, Håkansson and Lindgreb[6] reported that the EEG of patients with brain tumors was normalized during the first half of the daily therapeutic X-irradiation. Girgor'yev[5] also pointed out that the changes of the photic EEG response and the EEG activity of human patients which occurred within 2 hours after a single irradiation gradually disappeared during the course of additional radiation therapy. From the results of cats irradiated with 0.3 to 20 kR, accumulated according to various exposure schedules, Schoenbrun *et al.*[20] reported that there was radiation tolerance to fractionated doses in the central nervous system. The results reported here indicate that repeated irradiation had cumulative effects on the brain electrical activity. The differences noted between our studies and those of the above workers could be based on differences in experimental design and techniques.

Delayed effects of fractionated irradiation

We have found no consistent results in the changes of the AEP after final exposure. In one of three subjects, the amplitude of the AEP decreased on the 130th day after exposure. Although there is little information available in the literature about the changes of brain electrical activity after repeated exposure, electrophysiological studies on long term effects after a single ionizing radiation have been made by many workers[8][10][12][19]. Ross *et al.*[19] stated that the EEG of monkeys showed focal abnormalities consisting either of continuous, slow activity or of burst of fast, high amplitude wave up to 8 months after head irradiation with 1,500 R. The third and the fourth surface positive waves of the visual cortical response were altered markedly 2 days to 2 years after irradiation with massive doses of protons or deutrons[14]. We have reported that the visual evoked potential of rabbits irradiated with 250 R and 500 R decreased on day 10 after exposure[17]. From the above considerations, it seems likely that the effects of repeated irradiation last for a long time after exposure.

The present experiments did not give us enough information considering the mechanism of repeated irradiation on brain electrical activity. These aspects are being currently investigated in adult rabbits.

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